

临床研究

通塞颗粒对老年慢性阻塞性肺疾病急性加重期患者细胞外基质和粘附分子的影响

李素云¹ 李建生¹ 马利军² 李成海² 程先宽¹

摘要 目的:探讨老年慢性阻塞性肺疾病(COPD)急性加重期血清细胞外基质(ECM)和粘附分子的变化意义及通塞颗粒对其影响。方法:56例COPD急性加重期患者分为治疗组和对照组。治疗组在对照组治疗(西医综合治疗)的基础上,口服中药通塞颗粒。检测COPD患者治疗前后血清中细胞外基质成分和粘附分子的水平,并与20例健康老年人进行比较。结果:COPD急性加重期患者血清I型胶原(CⅠ)、Ⅲ型胶原(CⅢ)、Ⅳ型胶原(CⅣ)、可溶性细胞间粘附分子-1(ICAM-1)、E-选择素均明显高于健康老年人($P<0.01$);治疗后,治疗组CⅠ、CⅢ、CⅣ、ICAM-1、E-选择素水平和对照组CⅢ均明显降低($P<0.01$ 或 $P<0.05$),治疗组治疗后上述指标的降低较对照组显著($P<0.01$)。结论:细胞外基质和粘附分子的变化参与老年COPD急性加重期病理过程,中药通塞颗粒降低细胞外基质和粘附分子变化可能是该方治疗老年COPD的主要机制之一。

主题词 肺疾病,慢性阻塞性/中医药疗法 肺疾病,慢性阻塞性/血液 @ 通塞颗粒

慢性阻塞性肺疾病(COPD)是老年人的常见病,其致残率、死亡率较高,严重影响老年人的生活质量。细胞外基质(ECM)和粘附分子(AM)的变化与COPD的发生发展有着密切关系^[1~3]。本研究在通塞颗粒治疗COPD急性发作的基础上,观察该药对细胞外基质和粘附分子的影响,以探讨其作用机制。

1 临床资料

1.1 诊断标准:西医诊断标准参照中华医学会呼吸系统疾病学会(CSRD)1997年制定的《慢性阻塞性肺疾病诊治规范(草案)》中的诊断标准^[4]。COPD急性加重期诊断标准参照中华医学会呼吸系统疾病学会1997年制定的《慢性阻塞性肺疾病(COPD)诊治规范(草案)》和慢性阻塞性肺疾病全球倡议(GOLD)^[5]制定。COPD疾病严重程度分级标准参照CSRD对COPD的分级标准分为Ⅰ级、Ⅱ级、Ⅲ级^[4]。中医辨证标准参照

1993年卫生部颁布的《中药(新药)临床研究指导原则》第一辑^[6]和国家中医药管理局《中医临床病证诊断疗效标准》^[7]。纳入病例标准:凡确诊为COPD并且处于急性加重期,中医辨证符合痰(热)瘀阻肺证者即可纳入试验病例。排除病例标准:合并有结核、肿瘤等及其它肺部原发性疾病;合并严重心功能不全者(心功能三级以上);合并其它疾病如心血管、泌尿、消化、造血、内分泌代谢等系统严重疾病,肝、肾功能不全,精神病患者;对本药过敏者;不符合纳入标准,未按规定用药,无法判断疗效或资料不全影响疗效或安全性判断者。

1.2 一般资料:20名健康老年人作为参加河南中医学院第一附属医院体检者,胸透、B超、心电图、血尿便常规及血生化各项检查均正常,并排除1个月内有感染性疾病者。其中男12例,女8例,年龄60~73岁,平均 68.8 ± 3.32 岁。符合中华医学会老年医学学会对健康老年人标准的建议(修订草案,1995年)^[8]。60例COPD急性加重期患者来自2001年1~10月河南中医学院第一附属医院和河南省人民医院老年病研究中心的呼吸内科住院病人,剔除资料不全、未按规定服药等4例,符合研究要求的共56例,其中男41例,女15例,年龄60~73岁(71.16 ± 5.89),病程6~34年(18.90 ± 3.90);根据患者年龄、病程、病情程度等,随机分为两组。治疗组29例,男21例,女8例,年龄61~74岁(71.66 ± 4.75),病程 18.38 ± 1.05 年;对照组27例,男20例,女7例,年龄60~72岁(70.63 ± 6.96),病程 19.41 ± 6.61 年。病情轻度9例,治疗组5例,对照组4例;中度36例,治疗组、对照组各18例;重度11例,治疗组6例,对照组5例。

2 治疗及观察方法

2.1 给药方法:两组病人均根据病情及痰培养情况,给予支气管扩张剂(氨茶碱0.5g/d,静脉滴注,每日1次)、抗菌药物(头孢哌酮4.0g/d联合左旋氧氟沙星0.3g/d静脉滴注,每日1次)、控制性氧疗等综合治疗,必要时(严重的呼吸困难伴有辅助呼吸肌肉运动和反常腹部呼吸运动;呼吸频率 >35 次/分; $\text{PaO}_2<40\text{mmHg}$ 或 $\text{PaO}_2/\text{FiO}_2<200\text{mmHg}$;pH <7.25 和高

基金项目:河南省高校创新人才培养基金(2000-10)、河南省科学技术攻关项目(001170711)

1 河南中医学院老年医学研究所、第一临床医学院呼吸科、郑州市金水大道东段(450003)

2 河南省人民医院老年病中心呼吸科

收稿日期:2003-02-11;修回日期:2003-02-27

表 1 两组治疗前后血清 CⅠ、CⅢ、CⅣ变化比较($\bar{x} \pm s$)

组别	例数	CⅠ (ng/ml)	CⅢ (ng/ml)	CⅣ (μg/L)
健康组	20	12.100±3.165	15.150±2.368	53.635±8.164
COPD 组	56	127.625±13.894*	44.177±5.789*	88.602±13.879*
治疗组	治疗前 29	128.638±14.353	43.880±5.249	88.469±13.820
	治疗后 29	65.517±14.730*△	21.959±5.966*△	75.748±5.943*△
对照组	治疗前 27	126.611±12.981	44.474±5.568	88.733±13.386
	治疗后 27	119.759±16.201	36.019±6.283*	83.960±12.940

与健康组比较, * $P<0.01$; 与本组治疗前比较, △ $P<0.01$

碳酸血症 $\text{PaCO}_2 > 60\text{mmHg}$, 嗜睡、神志障碍等情况下)给以机械通气治疗(治疗组 2 例, 对照组 3 例)。治疗前 15 天及观察期间不使用糖皮质激素。治疗组在以上治疗的基础上, 口服中药通塞颗粒(由河南中医学院第一附属医院药剂科提供, 批号 01346, 由葶苈子、地龙、赤芍、川贝母、生晒参、麦冬、炙麻黄、制大黄、石菖蒲等组成, 每克颗粒剂相当于原生药 5.78g), 每次 6g, 每日 3 次; 每 7 天为 1 个疗程, 共观察 2 个疗程。

2.2 观察指标: 取清晨空腹静脉血, 制备血清, -40°C 低温冰箱保存, 待测有关指标。I 型胶原(CⅠ)、Ⅲ型胶原(CⅢ)采用双抗体夹心法测定, 试剂盒购自上海森雄工业公司(批号 0103159, 0104168), 单位以 ng/ml 表示。采用放射免疫法测定Ⅳ型胶原(CⅣ), 试剂盒购自上海海军医学研究所(批号 20019013), 单位以 μg/ml 表示。采用双抗体夹心法检测可溶性细胞间粘附因子(sICAM-1)和可溶性 E-选择素(sE-SLT), 试剂盒购于上海森雄科技实业有限公司(sICAM-1 批号为 0104160, sE-SLT 批号为 0104166), 单位以 pg/ml 表示。

2.3 统计学处理: 所有数据采用 SPSS 10.0 统计软件进行处理, 以均数±标准差($\bar{x} \pm s$)表示, 组间比较采用 t 检验。

3 治疗结果

3.1 两组细胞外基质变化比较: 见表 1, COPD 急性加重期患者血清 CⅠ、CⅢ、CⅣ水平均明显高于健康组($P<0.01$)。治疗后治疗组 CⅠ、CⅢ、CⅣ水平和对照组 CⅢ水平均明显降低($P<0.01$, $P<0.05$), 治疗组治疗后 CⅠ、CⅢ、CⅣ水平的降低较对照组显著($P<0.01$)。

3.2 两组血清可溶性 sE-SLT、sICAM-1 变化比较: 见表 2。COPD 急性加重期患者血清 sE-SLT、sICAM-1 水平均明显高于健康人($P<0.01$); 与治疗前比较, 治疗组治疗后 sE-SLT、sICAM-1 水平明显降低($P<0.01$), 对照组 sE-SLT 水平明显降低($P<0.01$); 治疗组治疗后 sE-SLT、sICAM-1 水平较对照组降低明显($P<0.01$)。

表 2 两组治疗前后血清 sE-SLT、sICAM-1 变化比较($\bar{x} \pm s$)

组别	例数	sE-SLT (pg/ml)	sICAM-1 (ng/ml)
健康组	20	2343.000±303.456	65.800±11.839
COPD 组	56	6292.167±1731.045*	239.489±73.425*
治疗组	治疗前 29	6261.724±1756.230	240.648±68.079
	治疗后 29	2899.655±509.534*△	158.490±35.681*△
对照组	治疗前 27	6322.593±1703.845	238.326±74.820
	治疗后 27	4358.519±610.124*	212.624±43.505

与健康组比较, * $P<0.01$; 与本组治疗前比较, △ $P<0.01$

4 讨论

ECM 是一组具有特殊功能与结构的大分子蛋白, 机体的 ECM 一般由胶原、蛋白聚糖和糖蛋白构成, 对组织细胞起机械性支持作用, 并影响细胞形状、控制细胞生长、增殖、分化、迁移、代谢及功能, 调节细胞的运动, 参与许多病理过程。COPD 患者肺部中性粒细胞和巨噬细胞聚集、活化和释放大量包括基质金属蛋白酶(MMPs)在内的分子, 过度释放的 MMPs 可引起呼吸道间质的改变和基底膜的毁损, 降解肺部 I、Ⅲ、Ⅳ型胶原^[9]以及呼吸道基底膜的主要组成部分——Ⅳ型胶原和不溶性弹性蛋白。COPD 晚期由于长期慢性缺氧常合并肺动脉高压, 肺血管结构重建是肺动脉压力持续增高的主要原因, 胶原的沉积增多与肺动脉高压形成和维持关系密切^[10,11]。本组资料表明, COPD 急性加重期患者外周血中 I、Ⅲ、Ⅳ型胶原水平明显增高, 表明 I、Ⅲ、Ⅳ型胶原参与了 COPD 的病理过程, 可能是由于 COPD 急性加重期肺内的急性炎症导致了胶原的代谢异常, 促进了 COPD 的气道重塑进程。因此, 调节胶原代谢的药物将会延缓 COPD 的这一病理过程。本结果表明, 经清热涤痰活血、宣肺降气平喘的中药通塞颗粒治疗后, 患者血清 I、Ⅲ、Ⅳ型胶原均有所降低, 该方药具有调节 COPD 急性加重期胶原代谢的作用, 其作用机制可能与其调节间质胶原酶、明胶酶系统有关。

AM 是一类介导细胞与细胞、细胞与细胞外基质相互粘附的糖蛋白, 维持机体正常防御功能。病理情况下, 参与许多炎症防御和损伤过程。炎症细胞在气道壁、管腔、肺泡内大量聚集是 COPD 发病的中心环节,

AM介导了COPD发病过程中炎细胞跨内皮迁移及向炎症部位积聚的过程,参与了炎细胞的活化^[12]。ICAM-1和E-SLT在COPD炎症细胞聚集、炎细胞活化、炎症介质释放、气道重塑病理过程中可能起着多种调节作用^[1,2]。本组资料表明,COPD急性加重期外周血中sE-SLT、sICAM-1水平明显高于健康人,可能是COPD急性加重期患者的感染刺激内皮细胞而产生大量sE-SLT和sICAM-1,增强白细胞与内皮细胞粘附,使其相互激活,产生和释放多种生物活性物质如蛋白酶和氧自由基等加重肺损伤。通过上述途径加重气道阻塞和炎症,使管腔进一步狭窄和肺泡壁结构破坏加速。通塞颗粒明显降低COPD急性加重期患者sE-SLT、sICAM-1水平,表明该药可能通过阻止白细胞与内皮细胞的粘附、减低炎细胞的活化、抑制炎症介质的释放等,而减轻炎症反应,这可能是该方治疗COPD的机制之一。

参考文献

- Hautamaki RD, Kobayashi DK, Senior RM, et al. Requirement for macrophage elastase for cigarette smoke induced emphysema in mice. *Science*, 1997, 277(5334):2002-2004.
- Schaberg T, Rau M, Stephan H, et al. Increased number of alveolar macrophages expressing surface molecules of the CD11/CD18 family in sarcoidosis and idiopathic pulmonary fibrosis is related to the production of superoxide anions by these cells. *Am Rev Respir Dis*, 1993, 147(6 Pt 1):1507-1513.
- Lazaar AL, Reitz HE, Panettieri RA Jr, et al. Antigen receptor-stimulated peripheral blood and bronchoalveolar lavage-derived T cells induce MHC class II and ICAM-1 expression on human airway smooth muscle. *Am J Respir Cell Mol Biol*, 1997, 16(1):38-45.
- 中华医学会呼吸疾病分会. 慢性阻塞性肺疾病(COPD)诊治规范(草案). *中华呼吸和结核杂志*, 1997, 20(4):199-203.
- Pauwels RA, Buist AS, Calverley PM, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med*, 2001, 163(5):1256-1276.
- 中华人民共和国卫生部. 中药(新药)临床研究指导原则(第一辑). 1993:1-5.
- 国家中医药管理局. 中医病证诊断疗效标准. 南京:南京大学出版社, 1994:4-5.
- 中华医学会老年医学学会. 中华医学会老年医学学会对健康老年人标准的建议(修订案). *中华老年医学杂志*, 1996, 15(1):9.
- Welgus HG, Jeffrey JJ, Eisen AZ. The collagen substrate specificity of human skin fibroblast collagenase. *J Biol Chem*, 1981, 256(18):9511-9515.
- Tozzi CA, Christiansen DL, Poiani GJ, et al. Excess collagen in hypertensive pulmonary arteries decreases vascular distensibility. *Am J Respir Crit Care Med*, 1994, 149(5):1317-1326.
- Durmowicz AG, Parks WC, Hyde DM, et al. Persistence, reexpression, and induction of pulmonary arterial fibronectin, tropoelastin, and type I procollagen mRNA expression in neonatal hypoxic pulmonary hypertension. *Am J Pathol*, 1994, 145(6):1411-1420.
- 殷少军. 粘附分子在变态反应性炎症中的作用. 国外医学生理病理科学与临床分册, 1995, 15(3):165-167.

多快好省煎好药

紫外线动态空气杀菌机

强力杀菌功能:

85%以上的紫外线波长是253.7nm,杀菌率高达99.9%

动态杀菌:

人机共处,可24小时运转;不妨碍日常生活,避免空气二次污染

特点:

1. 噪音小≤36Db(A)
2. 能耗低
3. 效果好
4. 寿命长(灯管可以使用8000小时)

适用:

《消毒技术规范》规定的II、III类卫生环境,实验室、制药厂等其他需要杀菌的场所。

东华煎药包装设备

6大系列
25个品种
30个办事处
100位维修工程师
3,000家医院药店正在使用
10,000名终端用户见证了
东华10年的奋斗历程

东华原医疗
DONGHUAYUAN MEDICAL

北京东华原医疗设备有限责任公司
电话: 010-89718013
邮编: 102200

地址: 北京市中关村昌平科技园区振超路1号
传真: 010-89718021
网址: www.donghuagroup.com

垂询热线: 800-810-0359

ABSTRACTS FROM ORIGINAL ARTICLES

Effects of Tongsai Granules on Extracellular Matrixes and Adhesion Molecule in the Patient of Senile Chronic Obstructive Pulmonary Diseases at the Acute Exacerbation Stage

Li Suyun, Li Jiansheng, Ma Lijun, et al.

Objective: To explore changes of serum extracellular matrixes and adhesion molecule and Tongsai Granules on them in the patient of senile chronic obstructive pulmonary disease (COPD) at acute exacerbation stage. **Methods:** 56 cases of COPD at exacerbation stage were divided into treatment group and control group. The treatment group was treated by oral administration of Tongsai Granules on the basis of the same treatment for the control group. Serum levels of extracellular matrixes components and adhesion molecule before and after treatment were detected, and 20 healthy old people were taken as comparison. **Results:** Serum levels of collagen type I (C I), collagen type III (C III) and collagen type IV (C IV), soluble intracellular adhesion molecular-1 (ICAM-1), E-selectin in the patient of COPD at the exacerbation stage were significantly higher than those in the healthy old people ($P < 0.01$). After treatment, serum levels of C I, C III, C IV, ICAM-1 and E-selectin in the treatment group and C III level in the control group were significantly decreased ($P < 0.01$ or $P < 0.05$). The decreases of the above indexes in the treatment group were more significant than those in the control group ($P < 0.01$). **Conclusion:** Extracellular matrixes and adhesion molecule are involved in the pathological process of senile COPD at the acute exacerbation stage, and decreases of extracellular mixtrixes and adhesion molecule induced by Chinese herbs Tongsai Granules is possibly one of the main mechanisms of the recipe for treatment of senile COPD.

Author's address: Institute of Seline Medicine, Henan TCM College, Zhengzhou 450003

Key words: Pulmonary diseases, chronic obstructive/TCM therapy; Pulmonary diseases, chronic obstructive/blood; @Tongsai Granules

(Original article on page 906)

Effects of Shenqi Fuxin Oral Liquid on Plasma Kaliuretic Peptide and Left Ventricular Replasticity in the Patient of Chronic Cardiac Functional Insufficiency after Myocardial Infarction

Ma Lu, Lei Yan, Wang Shiwen, et al.

Objective: To observe effects of Shenqi Fuxin Oral Liquid on plasma kaliuritic peptide (KP), cardiac function and left ventricular replasticity. **Methods:** 80 cases of chronic cardiac functional insufficiency after myocardial infarction were randomly divided into treatment group ($n = 44$) and control group ($n = 36$). Both groups were given the same routine treatment, and the treatment group was added with Shenqi

Fuxin Oral Liquid and the control group with Captopril. Plasma KP, endothelin-1 (ET-1) and atrial natriuretic polypeptide (ANP) before and after treatment were determined, and 6 months later, changes of the left ventricular replasticity and cardiac function were investigated by color ultrasound cardiogram. **Results:** Total effective rate was 86.1% in the treatment group and 90.3% in the control group with no significant difference between two groups ($P > 0.05$). After treatment the indexes of the cardiac replasticity and cardiac function in both groups improved significantly ($P < 0.01$), and ANP and ET-1 levels significantly decreased as compared with those before treatment ($P < 0.01$ or $P < 0.05$). After treatment, KP level in the treatment group decreased significantly as compared with that before treatment ($P < 0.05$), and in the control group it did not change significantly ($P > 0.05$). **Conclusion:** Shenqi Fuxin Oral Liquid can decrease plasma KP level and has functions of arresting cardiac replasticity, improving cardiac function in the patient of chronic cardiac functional insufficiency after myocardial infarction.

Author's address: Institute of Cardiovascular Diseases, General Hospital of PLA, Beijing 100853

Key Words Myocardiac infaction/TCM therapy; @ Shenqi Fuxin Oral Liquid

(Original article on page 909)

Effects of Luohuo Capsules on Dynamic Blood Pressure and Life Quality in the Patient of Hypertention

Yu Xiangdong, Zhou Wenquan, Cui Ling, et al.

Objective: To observe clinical therapeutic effect of Luohuo Capsules. **Methods:** 90 cases of hypertension were randomly divided into treatment group ($n = 60$) and control group ($n = 30$). The treatment group was treated with Luohuo Capsules and the control group with Beijing Jiangya No. 0 for 4 therapeutic course, and safety, clinical symptoms, blood pressure, dynamic blood pressure of 24 hours (ABPM) and life quality were investigated. **Results:** The total effective rate was 85.0% in the treatment group and 86.6% in the control group with no significant difference between groups ($P > 0.05$). The treatment group in the improvement of most clinical symptoms were superior to the control group ($P < 0.05$ or $P < 0.01$). Luohuo Capsules could decrease ABPM and improve life quality of the patient. **Conclusion:** Luohuo Capsules are safe with no reverse effect for treatment of hypertension grade I and II.

Author's address: Xuanwu Hospital, Capital Medical University, Beijing 100053

Key words: Hypertension/TCM therapy; Blood pressure/drug effect; @Luohuo Capsules

(Original article on page 912)