

doi: 10.13241/j.cnki.pmb.2017.09.018

炎症性肠病患者的自主神经功能研究

谭丽^{1,2} 刘小伟^{1Δ} 申月明² 曾亚² 陈伟²

(1 中南大学湘雅二医院 湖南 长沙 410011; 2 长沙市中心医院 湖南 长沙 410004)

摘要 目的:探讨炎症性肠病患者的自主神经功能状态。**方法:**选取炎症性肠病(IBD)患者 60 例作为观察组,包括活动期溃疡性结肠炎(UC)37 例,活动期克罗恩病(CD)23 例,同期健康体检者 50 例作为对照组。交感神经功能采用握力试验以及卧立位血压差的方式进行检查;迷走神经功能则采用卧立位心率变化和 Valsalva 动作反应指数检查方法。**结果:**① 观察组卧立位心率变化均值明显低于对照组,其中溃疡性结肠炎和克罗恩病心率变化均值均明显低于对照组,差异有统计学意义($P<0.05$);溃疡性结肠炎与克罗恩病心率变化均值差异无统计学意义($P>0.05$);溃疡性结肠炎和克罗恩病 Valsalva 动作反应指数与对照组相比差异无统计学意义($F=1.06, P>0.05$)。② 观察组卧立位血压差均值明显高于对照组,握力试验的血压反应均值明显低于对照组,溃疡性结肠炎和克罗恩病卧立位血压差均值均明显低于对照组,握力试验的血压反应均值均明显低于对照组差异有统计学意义($P<0.05$);而溃疡性结肠炎和克罗恩病卧立位血压差均值及血压反应均值比较均无统计学差异。**结论:**炎症性肠病患者存在自主神经功能紊乱,交感神经功能增强而迷走神经功能相对减弱。

关键词:炎症性肠病;溃疡性结肠炎;克罗恩病;自主神经

中图分类号:R574.62 **文献标识码:**A **文章编号:**1673-6273(2017)09-1671-03

Research on the Autonomic Nervous Function of Patients with Inflammatory Bowel Disease

TAN Li^{1,2}, LIU Xiao-wei^{1Δ}, SHEN Yue-ming², ZENG Ya², CHEN Wei²

(1 The Second Xiangya Hospital of Central South University, Changsha, Hunan, 410011, China;

2 Changsha Central Hospital, Changsha, Hunan, 410004, China)

ABSTRACT Objective: To investigate the status of autonomic nervous function in patients with inflammatory bowel disease. **Methods:** 60 cases of patients with inflammatory bowel disease (BD) were chosen as the observation group, including 37 cases of active ulcerative colitis (UC) and 23 cases of active Crohn's disease (CD); in the same period, 50 healthy persons were selected as the control group. The autonomic nervous functions of the patients were detected: sympathetic nerve function by handgrip test and postural difference of blood pressure by way of lying and standing blood pressure difference; vagus nerve function was examined through the change of heart rate in lying position as well as the Valsalva action response index. **Results:** ① In the observation group, the change of heart rate was significantly lower than that of the control group ($P<0.05$); the mean value of heart rate in patients with ulcerative colitis and Crohn's disease were dramatically lower than that in the control group ($P<0.05$). There was no significant difference between the observation group and the control group ($P>0.05$) in the Valsalva action response index of ulcerative colitis and Crohn's disease in the observation group. ② The difference of blood pressure in the observation group was significantly higher than that in the control group ($P<0.05$). The mean difference of blood pressure in the patients with ulcerative colitis and Crohn's disease was significantly lower than that in the control group ($P<0.05$); there was no significant difference in the mean blood pressure difference between ulcerative colitis and Crohn's disease ($P>0.05$). The mean blood pressure response to handgrip test in observation group was significantly lower than the control group ($P<0.01$). The mean blood pressure response of ulcerative colitis and Crohn's disease grip test were significantly lower than the control group ($P<0.01$), while there was no significant difference between the two groups mean blood pressure response to the handgrip test ($P>0.05$). **Conclusion:** Autonomic nerve dysfunction existed in patients with inflammatory bowel disease: sympathetic nerve function was enhanced, while the vagus nerve function was relatively weakened.

Key words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Autonomic nerve

Chinese Library Classification(CLC): R574.62 **Document code:** A

Article ID: 1673-6273(2017)09-1671-03

作者简介:谭丽(1980-),女,硕士研究生,主治医师,研究方向:炎

症性肠病,电话:18073181831, E-mail: thinkmail3@163.com

Δ 通讯作者:刘小伟,主任医师,博士生导师,

E-mail: liuxw@csu.edu.cn

(收稿日期:2016-10-12 接受日期:2016-10-30)

前言

炎症性肠病是常见的肠道疾病,近年来发病率一直处于升高趋势^[1]。目前炎症性肠病的发病机制仍不清楚,多数学者认为其与环境、遗传、免疫异常和感染有关^[2]。有研究显示炎症性肠病患者存在一定的自主神经功能障碍,包括自主神经功能损伤以及神经递质释放问题^[3,4]。也有研究显示对小鼠自主神经进行破坏容易引起其出现腹泻、便血等肠道炎症反应的临床表现^[5]。本研究通过观察炎症性肠病患者的自主神经功能,探讨炎症性肠病与自主神经紊乱的相关性,现报道如下。

1 资料与方法

1.1 一般资料

选取我院消化内科住院以及门诊患者 60 例作为观察组,男 38 例,女 22 例,年龄(20~64)岁,平均年龄(39.52± 10.52)岁。其中,溃疡性结肠炎 37 例,克罗恩病 23 例。患者符合中华医学会关于 IBD 诊治指南,并且病情程度采用 Truelove-Witts 标准^[6]。病情程度:轻度 33 例,中度 27 例;大便次数(0~2)次/天 5 例,(3~6)次/天 48 例,≥ 7 次 7 例。对照组选用同期在门诊进行体检的健康人 50 例,男 26 例,女 24 例,年龄(22~65)岁,平均年龄(40.17± 9.25)岁。两组患者性别、年龄差异无统计学意义,具有可比性。

排除标准:① 患者为放射性结肠炎、缺血性结肠炎、肠结核、阿米巴痢疾、细菌性痢疾、慢性血吸虫病等结肠炎患者;② 患者在孕期或者正在服用影响神经系统类药物;③ 患者本身存在神经系统疾病、自身免疫系统疾病、内分泌疾病等可能影响实验结果的病患。

1.2 神经功能检测

1.2.1 迷走副交感神经功能检测 ① 卧立位心率变化:患者体位选卧位,静息 2 min 后行心电图检测,记录数值后起立 1-3 min,再行心电图检测,反复进行 30 次。计算站立后第 30 次心动周期 RR 间期与第 15 次心动周期的 RR 间期之比值(2:1),正常人正常值 >1.04,比值 <1.00 表示迷走神经功能障碍;正常值

界限按年龄分配,其中相关为 30-49 岁为 1.17;40-49 岁为 1.09;50-65 岁为 1.03;② Valsalva 动作反应指数:患者平躺后,嘱进行深吸气后用力吹与血压计相连的橡皮管,当血压计水银柱上升 40 mmHg 后,坚持 15 s 再放松,之间用心电监护仪器记录动态心电图,间隔 1 min,重复上述过程 3 次。测定试验中 IV 期最长 RR 间期 / II 期最短 RR 间期的比值,即为此动作时最快心率 / 放松时最慢心率比值,即瓦氏指数。其正常值 >1.45,比值 <1.2 则为阳性^[7]。

1.2.2 交感肾上腺能神经功能检测 ① 卧立位血压差:患者处卧位静息 20 min 后进行血压测定并记录血压值,然后起立 1-3 min,同时测量立位血压。计算立位与卧位的 SBP 差值。正常值为直立 3 min 内,收缩压下降 ≤ 20 mmHg,血压变化 >30 mmHg 为阳性;② 握力试验的血压反应:患者在静息状态下进行血压测定三次取平均值,然后患者使用握力计以不同握力握住握力计并坚持 5 min,在握持时进行血压测量,每次换不同力量时要间隔 1 min。测出握力时最高的舒张压(DBP)与 3 次握力前的平均 DBP 的差值。DBP 差值 >15 mmHg 为正常,差值 <10 mmHg 为阳性^[8]。

1.3 统计学分析

应用 SPSS20.0 统计软件包进行统计分析,正态分布的各统计指标均以均数± 标准差($\bar{x} \pm s$)表示,多组间比较采用方差分析,两组间数值比较采用 t 检验,以 P<0.05 为差异具有统计学意义。

2 结果

2.1 两组患者迷走副交感神经功能对比

观察组卧立位心率变化均值明显低于对照组,差异有统计学意义(P<0.05)。其中,溃疡性结肠炎和克罗恩病心率变化均值均明显低于对照组,差异有统计学意义(P<0.05);溃疡性结肠炎与克罗恩病心率变化均值差异无统计学意义(P>0.05)。观察组中溃疡性结肠炎和克罗恩病 Valsalva 动作反应指数与对照组相比,差异无统计学意义(P>0.05)。

表 1 两组患者卧立位心率变化均值和 Valsalva 动作反应指数对比

Table 1 Comparison of the mean value of heart rate changes in lying position and Valsalva action response index between two groups

Groups	n	Heart rate changes in lying position	Valsalva action response index
Observational-group	60	0.95± 0.04*	1.27± 0.07
Ulcerative colitis	37	0.96± 0.04*	1.25± 0.06
Crohn's disease	23	0.95± 0.05*	1.29± 0.07
Control-group	50	1.08± 0.06	1.30± 0.08

Note: *P<0.05 compared with control group.

2.2 两组患者交感神经功能对比

观察组卧立位血压差均值明显高于对照组,差异有统计学意义(P<0.05)。其中,溃疡性结肠炎和克罗恩病卧立位血压差均值均明显高于对照组,差异有统计学意义(P<0.05);溃疡性结肠炎与克罗恩病卧立位血压差均值差异无统计学意义(P>0.05)。观察组握力试验的血压反应均值明显低于对照组,差异无统计学意义(P<0.01),溃疡性结肠炎和克罗恩病握力试验的血压反应均值均明显低于对照组,差异有统计学意义(P<0.01),而两组

间握力试验的血压反应均值差异则无统计学意义(P>0.05)。

3 讨论

自主神经系统是支配的肠道的主要神经,其发送功能紊乱极有可能同时引起患者出现肠道功能紊乱,可能是诱发炎症性肠病的主要原因之一^[9-11]。Lindgren S 等对炎症性肠病患者进行神经功能检测以及对动物实施实验性结肠炎均发现炎症性肠病患者会出现自主神经系统功能失调,主要表现为迷走神经出

表 2 两组患者卧立位血压差均值和握力试验的血压反应均值对比

Table 2 Comparison of the mean value of blood pressure difference in lying position and blood pressure response of handgrip test between two groups

Groups	n	Blood pressure difference in lying position	Blood pressure response of handgrip test
Observational-group	60	27.93± 3.22*	8.62± 2.77 [#]
Ulcerative colitis	37	28.46± 3.94*	9.25± 2.81 [#]
Crohn's disease	23	27.66± 3.21*	8.55± 2.37 [#]
Control-group	50	24.08± 3.06	14.22± 3.08

Note: *P<0.05, [#]P<0.01 compared with control group.

现损伤并伴有迷走神经功能障碍,而交感神经则出现功能增强^[12,13]。此外,研究显示炎症性肠病患者存在神经递质分泌障碍,主要表现为迷走神经分泌的递质--乙酰胆碱出现明显的减少,乙酰胆碱具有阻止收到炎症因子刺激的细胞分泌细胞因子的作用,可以明显抑制炎症性肠病症状^[14-17]。国内也有实验显示儿茶酚胺在炎症性肠病中同样起十分重要的作用,炎症性肠病小鼠注射 $\alpha 2$ 肾上腺素受体拮抗剂后,其肠道中的炎症因子分泌大大减少,而给予 $\alpha 2$ 肾上腺素受体激动剂处理后的小鼠则出现相反的实验结果^[18]。这些研究结果均提示炎症性肠病患者存在自主神经功能紊乱。

卧立位心率和Valsalva动作反应指数是临床常用的对神经迷走的检测方法,有研究对糖尿病患者进行相关检测,发现出现卧立位心率和Valsalva动作反应指数异常患者均存在迷走神经紊乱^[19]。本研究在对炎症性肠病患者进行卧立位心率检测和Valsalva动作反应指数测定对比,发现炎症性肠病患者卧立位心率明显低于对照组,但是Valsalva动作反应指数与对照组无明显差异,因此炎症性肠病出现迷走副交感的紊乱不是绝对减弱,而是相对减弱。另外,本研究还显示患者卧立位血压差值和握力试验之血压反应差值与正常对照组差异有统计学意义,说明在炎症性肠病期间,患者交感肾上腺素功能是增强的。国外也有相关研究报道炎症性肠病患者存在明显的交感神经功能增强^[20]。本研究结果与国外研究报道一致。

综上所述,炎症性肠病患者存在交感神经和迷走神经紊乱,具体表现在交感神经功能增强,迷走神经功能减弱,对患者神经功能进行检测能够帮助临床上对炎症性肠病的诊断以及治疗效果评估。

参考文献(References)

- [1] Kim D H, Cheon J H. Intestinal Behçet's Disease: A True Inflammatory Bowel Disease or Merely an Intestinal Complication of Systemic Vasculitis[J]. Yonsei Medical Journal, 2016, 57(1): 22-32
- [2] McMullen L, Leach S T, Lemberg D A, et al. Current roles of specific bacteria in the pathogenesis of inflammatory bowel disease [J]. AMC Microbiology, 2015, 1(1): 82-91
- [3] Le Loupp AG, Bach-Ngohou K, Bourreille A, et al. Activation of the prostaglandin D2 metabolic pathway in Crohn's disease: involvement of the enteric nervous system [J]. BMC Gastroenterol, 2015, 15(1): 1-11
- [4] Gheita T A, Gazzar I I E, El-Fishawy H S, et al. Involvement of IL-23 in enteropathic arthritis patients with inflammatory bowel disease: preliminary results[J]. Clinical Rheumatology, 2014, 33(5): 713-717
- [5] Talapka P, Nagy LI, Pál A, et al. Alleviated mucosal and neuronal

damage in a rat model of Crohn's disease [J]. World J Gastroenterol, 2014, 20(44): 16690-16697

- [6] 中华医学会消化病学分会炎症性肠病协作组. 对于我国炎症性肠病诊断治疗规范的共识意见[J]. 胃肠病学, 2007, 12(8): 488-495
Inflammatory bowel disease cooperation group of Digestive Disease Branch of Chinese Medical Association. The consensus of diagnosis and treatment standard for inflammatory bowel disease in China [J]. J Gastroenterology, 2007, 12(8): 488-495
- [7] Misteli H, Koh CE, Wang LM, et al. Myenteric plexitis at the proximal resection margin is a predictive marker for surgical recurrence of ileocaecal Crohn's disease[J]. Colorectal Dis, 2015, 17(4): 304-310
- [8] Willemze RA, Luyer MD, Buurman WA, et al. Neural reflex pathways in intestinal inflammation: hypotheses to viable therapy [J]. Nat Rev Gastroenterol Hepatol, 2015, 12(6): 353-362
- [9] Clarençon D, Pellissier S, Sinniger V, et al. Long term effects of low frequency (10 hz) vagus nerve stimulation on EEG and heart rate variability in Crohn's disease: a case report [J]. Brain Stimul, 2014, 7(6): 914-916
- [10] Zhang Y, Du X, Liu F, et al. The Effects of Guided Imagery on Heart Rate Variability in Simulated Spaceflight Emergency Tasks Performers[J]. Biomed Research International, 2014, 2015: 1-8
- [11] Bonaz B L, Bernstein C N. Brain-Gut Interactions in Inflammatory Bowel Disease[J]. Gastroenterology, 2013, 144(1): 36-49
- [12] Pellissier S, Dantzer C, Mondillon L, et al. Relationship between vagal tone, cortisol, TNF-alpha, epinephrine and negative affects in Crohn's disease and irritable bowel syndrome [J]. PLoS One, 2014, 9(9): e105328
- [13] Sallam M Y, El-Gowilly S M, Abdel-Galil A G A, et al. Central GABA A receptors are involved in inflammatory and cardiovascular consequences of endotoxemia in conscious rats [J]. Naunyn-Schmiedeberg's Archives of Pharmacology, 2016, 389(3): 279-288
- [14] Lindgren S, Stewenius J, Sjölund K, et al. Autonomic vagal nerve dysfunction in patients with ulcerative colitis [J]. Scand J Gastroenterol, 1993, 28(7): 638-642
- [15] Rahman A A, Robinson A M, Jovanovska V, et al. Alterations in the distal colon innervation in Winnie mouse model of spontaneous chronic colitis[J]. Cell & Tissue Research, 2015, 362(3): 1-16
- [16] Fritze D, Zhang W, Li J Y, et al. Thrombin mediates vagal apoptosis and dysfunction in inflammatory bowel disease [J]. J Gastrointest Surg, 2014, 18(8): 1495-1506
- [17] Fritze D, Zhang W, Li J Y, et al. TNF α Causes Thrombin-Dependent Vagal Neuron Apoptosis in Inflammatory Bowel Disease [J]. Journal of Gastrointestinal Surgery, 2014, 18(9): 1632-1641 (下转第 1630 页)

- [3] He L, Jiang Y, Su H, et al. Vascular Endothelial Function Assessed by Postischemic Diastolic Blood Pressure Is Associated with Acclimatization and Acute Mountain Sickness[J]. High Alt Med Biol, 2016, 17(1): 11-15
- [4] Johnson NJ, Luks AM. High-Altitude Medicine. Med Clin North Am [J]. 2016, 100(2): 357-369
- [5] Quigley I, Zafren K. Subtle cognitive dysfunction in resolving high altitude cerebral edema revealed by a clock drawing test[J]. Wilderness Environ Med, 2016, 10(1): 78-84
- [6] Khodae M, Grothe HL, Seyfert JH, et al. Athletes at High Altitude[J]. Sports Health, 2016, 8(2): 126-132
- [7] Horiuchi M, Endo J, Akatsuka S, et al. Prevalence of acute mountain sickness on Mount Fuji: A pilot study [J]. J Travel Med, 2016, 23(4): 1195-1982
- [8] YSh, Khalimov, Vetryakov, et al. Peculiarities of organisation and health care delivery to military servicemen under conditions of mid-and high mountains[J]. Voen Med Zh, 2016, 337(1): 29-35
- [9] He L, Jiang Y, Su H, et al. Vascular Endothelial Function Assessed by Postischemic Diastolic Blood Pressure Is Associated with Acclimatization and Acute Mountain Sickness[J]. High Alt Med Biol, 2016, 17(1): 11-15
- [10] 李西玲. 尿微量白蛋白测定对高原老年肺心病患者肾损害的早期诊断[J]. 中国老年学杂志, 2013, 33(18): 4603-4604
Li Xi-ling. The early diagnosis in elderly renal impairment of patients with high altitude pulmonary heart disease by of microalbuminuria[J]. Chinese Journal of Gerontology, 2013, 33(18): 4603-4604
- [11] 王琰, 努尔曼古丽, 王引虎. 进驻不同海拔高原健康男青年肾功能的变化[J]. 高原医学杂志, 2011, 21(3): 40-40
Wang Yan, Nu EMGL, Wang Yin-hu. The changes of renal function of healthy young men at different variations of altitude plateau[J]. Journal of High Altitude Medicine, 2011, 21(3): 40-40
- [12] 周齐全, 王福领, 郭鸿斌, 等. 高原低氧环境暴露对移居人群肾功能和尿液成分的影响 [J]. 中国病理生理杂志, 2010, 0(A10): 1972-1972
Zhou Qi-quan, Wang Fu-ling, Guo Hong-bin, et al. The effect of exposed to high altitude hypoxia environment on renal function and urine components of crowd moved[J]. Chinese Journal of Pathophysiology, 2010, 0(A10): 1972-1972
- [13] 吴彦氏, 杨聪. 高原慢性肾功能不全与血尿酸相关性分析[J]. 西南国防医药, 2011, 21(2): 172-173
Wu Yan-min, Yang Cong. The correlation analysis between plateau chronic renal insufficiency and serum uric acid [J]. Medical Journal of National Defending forces in Southwest China, 2011, 21(2): 172-173
- [14] Krzeminska E, Wyczalkowska-Tomasik A, Korytowska N, et al. Comparison of Two Methods for Determination of NGAL Levels in Urine: ELISA and CMIA[J]. J Clin Lab Anal, 2016, 13, [Epub ahead of print]
- [15] Oncel MY, Canpolat FE, Arayici S, et al. Urinary markers of acute kidney injury in newborns with perinatal asphyxia[J]. Ren Fail, 2016, 7(1): 1-7
- [16] Hanna M, Brophy PD, Giannone PJ, et al. S Early Urinary Biomarkers of Acute Kidney Injury in Preterm Infants [J]. Pediatr Res, 2016, 73(7): 863-869
- [17] 倪军, 王锦波, 洪刚, 等. 某部官兵赴高原训练期间尿蛋白水平变化观察[J]. 人民军医, 2013, 56(7): 753-754
Ni Jun, Wang Jin-bo, Hong Gang, et al. The level changes of urine protein in officers and soldiers at altitude training period [J]. People's Military Surgeon, 2013, 56(7): 753-754
- [18] 杨磊, 杨有利, 石自福. 尿微量蛋白联合检测对高原短期暴露人群返回低海拔地区后肾脏脱适应损伤的判定[J]. 中华实用诊断与治疗杂志, 2014, 28(6): 572-575
Yang Lei, Yang Yuo-li, Shi Zi-fu. Combined detection of urine microprotein in the diagnosis of kidney deadaptation injury in a population back to low altitude after a short-term exposure to high altitude [J]. Journal of Practical Diagnosis and Therapy, 2014, 28(6): 572-575
- [19] Mintzer DN, Leshem E, Chazan B, et al. High altitude exposure in travelers with preexisting medical conditions[J]. Harefuah, 2015, 154(11): 725-9, 741, 740
- [20] Feddersen B, Neupane P, Thanbichler F, et al. Regional differences in the cerebral blood flow velocity response to hypobaric hypoxia at high altitudes[J]. J Cereb Blood Flow Metab, 2015, 35(11): 1846-1851
- [21] Levine BD. Going High with Heart Disease: The Effect of High Altitude Exposure in Older Individuals and Patients with Coronary Artery Disease[J]. High Alt Med Biol, 2015, 16(2): 89-96
- [22] Kiyamu M, León-Velarde F, Rivera-Chira M, et al. Developmental Effects Determine Submaximal Arterial Oxygen Saturation in Peruvian Quechua[J]. High Alt Med Biol, 2015, 16(2): 138-146

(上接第 1673 页)

- [18] 沙丽娜, 李楠, 王艳梅. 炎症性肠病患者自主神经功能改变[J]. 临床和实验医学杂志, 2014, 13(9): 721-723
Sha Li-na, Li Nan, Wang Yan-mei. Changes of autonomic nervous function in patients with inflammatory bowel disease [J]. J Clinical and Experimental Medicine, 2014, 13(9): 721-723
- [19] Rubio A, Pellissier S, Picot A, et al. The link between negative affect, vagal tone, and visceral sensitivity in quiescent Crohn's disease [J]. Neurogastroenterol Motil, 2014, 26(8): 1200-1203
- [20] Sun P, Zhou K, Wang S, et al. Involvement of MAPK/NF- κ B signaling in the activation of the cholinergic anti-inflammatory pathway in experimental colitis by chronic vagus nerve stimulation[J]. PLoS One, 2013, 8(8): e69424