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曲美他嗪对慢性心力衰竭患者血管内皮功能的影响

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摘要 目的:研究曲美他嗪对慢性心力衰竭患者血管内皮功能的影响。**方法:**选择2013年1月~2015年12月在我院进行诊治的慢性心力衰竭患者158例为研究对象,采用奇偶数法随机分为两组,每组79例。对照组采用利尿、平衡电解质、扩血管、营养心肌等常规抗心衰治疗,观察组联合采用曲美他嗪治疗。分别于治疗前和治疗后1个月检测两组患者的血流介导血管舒张功能、内皮素-1水平、一氧化氮水平、心率、血压、白细胞计数、血肌酐和谷丙转氨酶水平。**结果:**治疗后,观察组的血流介导血管舒张功能明显高于治疗前($P<0.05$),且肱动脉内径和血流介导血管舒张功能均明显高于对照组($P<0.05$);两组血浆内皮素-1均较治疗前降低($P<0.05$),一氧化氮升高($P<0.05$),且观察组的血清内皮素-1水平明显低于对照组,血清一氧化氮水平明显高于对照组($P<0.05$);两组的心率、血压、肾功能、肝功能和血常规结果相比差异均无统计学意义($P>0.05$),且两组均无明显不良反应发生。**结论:**曲美他嗪可显著改善慢性心力衰竭患者的血管内皮功能,可能与其降低血浆内皮素-1水平、升高一氧化氮水平有关。

关键词:慢性心力衰竭;曲美他嗪;血管内皮功能

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Effects of Trimetazidine on the Vascular Endothelial Function of Patients with Chronic Heart Failure

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ABSTRACT Objective: To investigate the effect of trimetazidine on the vascular endothelial function of patients with chronic heart failure. **Methods:** 158 cases of patients with chronic heart failure who were treated in our hospital from January 2013 to December 2015 were selected and randomly divided into two groups. The control group was treated with diuresis, electrolyte balance, expanding blood vessels, nutrition myocardial, while the observation group was treated with conventional heart failure treatment combined with trimetazidine. The blood flow mediated vasodilatation function, serum levels of endothelin-1 levels, nitric oxide, heart rate, blood pressure, white blood cell count, serum creatinine and third transaminase levels were compared before and at 1 month after treatment. **Results:** After treatment, the blood flow mediated vasodilatation function of observation group was obviously higher than before treatment ($P<0.05$), and the brachial artery diameter and blood flow mediated vasodilatation function of observation group were significantly higher than those of the control group ($P<0.05$); the plasma endothelin-1 levels of both groups were significantly increased ($P<0.05$), the nitric oxide level were significantly decreased ($P<0.05$), and the endothelin-1 level of observation group was obviously higher than that of the control group ($P<0.05$), the nitric oxide level was significantly lower than that of the control group ($P<0.05$); the heart rate, blood pressure, kidney function, liver function and blood routine of two groups showed no obvious difference between two groups ($P>0.05$), and no obvious adverse reaction was found in both groups. **Conclusion:** Trimetazidine could improve the endothelial function of patients with chronic heart failure, which might be related to the decrease of plasma levels of endothelin-1 and elevation of the plasma levels of nitric oxide.

Key words: Chronic heart failure; Trimetazidine; Vascular endothelial function

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前言

慢性心力衰竭是由于各种心脏疾病造成的以机体运动耐

力下降、心脏功能不全、神经内分泌激活和心室重构为主要特征的临床综合征^[1]。近年来,随着我国人口老龄化的加速,高血压、冠心病等心血管疾病发病率的升高,心力衰竭的发病率亦在逐年攀升,且患者病情加重后1年内的病死率达40%^[2]。曲美他嗪可以改善心肌缺血,优化心肌能量代谢,是心血管疾病常用的辅助用药,具有既不增加心肌氧耗也不影响主要血液动力学的优点^[3,4]。研究显示曲美他嗪可以提高左室射血分数,降低左室容积,有效改善慢性心力衰竭患者的左心室收缩功能和舒张功能^[5],但关于其对于内皮功能影响的研究报道较为少见。本

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研究主要探讨了曲美他嗪对慢性心力衰竭患者血管内皮功能的影响,以期为临床治疗心力衰竭提供理论依据。

1 资料与方法

1.1 一般资料

选择 2013 年 1 月至 2015 年 12 月西安市中心医院 158 例慢性心力衰竭患者为研究对象,均符合有关慢性心力衰竭的诊断标准^[7],排除严重心律失常者、急性心力衰竭者、心源性休克者、有严重感染性疾病者、存在精神异常、不能不配合治疗、影响临床疗效评价的患者。将 158 例患者根据就诊先后顺序编号后,采用奇偶数法分为两组。观察组 79 例,男 47 例,女 32 例;年龄 55~82 岁,平均 (67.13±11.25) 岁;病程 1~6 年,平均 (4.25±2.13) 年;伴有高血压心脏病 7 例,冠心病 16 例,扩张型心肌病 2 例,风心病 3 例;心功能 NYHA 分级:II 级 25 例,III 31 例,IV 及 23 例。对照组 79 例,男 46 例,女 33 例;年龄 54~82 岁,平均 (66.35±12.38) 岁;病程 1~6 年,平均 (4.16±2.25) 年;伴有高血压心脏病 6 例,冠心病 18 例,扩张型心肌病 2 例,风心病 4 例;心功能 NYHA 分级:II 级 24 例,III 32 例,IV 及 23 例。两组一般资料比较差异均无统计学意义 ($P>0.05$),具有可比性。

1.2 治疗方法

对照组采用包括利尿、营养心肌、平衡电解质、扩血管、强心等常规抗心衰治疗,观察组联合口服曲美他嗪 20 mg/次,每天 3 次,疗程均为 1 个月。

1.3 观察指标

根据 2002 年美国心脏病学会公布的超声评价血流介导血管舒张功能指南^[8]对血流介导血管舒张功能进行评价。彩色多普勒超声诊断仪(厂家:美国 GE VOLUSON,型号:E10 型),探头频率设置为 7.5 MHz,轴向分辨率为 0.1 mm,患者取仰卧位,先检查肱动脉的纵向长轴,再进行图像采集。基础内径为患者静息状态下的内径,阻断动脉血流 5 min 后,迅速松开血压袖带,在放气 1 min 后测量肱动脉内径。血流介导血管舒张功能以(肱动脉内径-基础内径)/基础内径×100%表示。

分别于治疗前和治疗后 1 个月采集 4 mL 空腹肘静脉血,采用放射免疫法检测内皮素-1 水平,采用硝酸盐还原酶法检测一氧化氮水平;检测两组患者的心率、血压、白细胞计数、肌酐、谷丙转氨酶等,并记录治疗后的呕吐、恶心、变态反应、强直、震颤、运动不能等不良反应。

1.4 统计学分析

采用 SPSS15.00 软件,计量资料以 $\bar{x} \pm s$ 表示,组间对比用 t 检验,以 $P<0.05$ 表明差异有统计学意义。

2 结果

2.1 两组治疗后血流介导血管舒张功能比较

治疗后,观察组的血流介导血管舒张功能明显高于治疗前 ($P<0.05$),且观察组的肱动脉内径和血流介导血管舒张功能均明显高于对照组 ($P<0.05$),见表 1。

表 1 两组治疗前后血流介导血管舒张功能的比较($\bar{x} \pm s$)

Table 1 Comparison of the blood flow mediated vasodilatation function between two groups before and after treatment($\bar{x} \pm s$)

Groups	n		Basic inner diameter (mm)	Brachial artery diameter (mm)	Blood flow mediated vasodilatation function (%)
Control group	79	Before treatment	4.20±0.31	4.52±1.33	9.12±2.15
		After treatment	4.22±0.26	4.53±1.65	10.03±3.21
Observation group	79	Before treatment	4.21±0.35	4.54±1.42	9.13±2.58
		After treatment	4.25±0.43	4.82±1.54 ^a	11.85±3.27 ^{ab}

Note: Compared with control group, ^a $P<0.05$; Compared with before treatment, ^b $P<0.05$.

2.2 两组治疗前后血浆内皮素-1、一氧化氮水平的比较

治疗后,两组的血浆内皮素-1 水平均较治疗前显著降低 ($P<0.05$),一氧化氮水平均较治疗前显著升高 ($P<0.05$),且观察

组的血浆内皮素-1 水平显著低于对照组,血浆一氧化氮水平明显高于对照组 ($P<0.05$),见表 2。

表 2 两组治疗前后血浆内皮素-1、一氧化氮水平的比较($\bar{x} \pm s$)

Table 2 Comparison of the plasma levels of endothelin-1 and NO levels between two groups before and after treatment ($\bar{x} \pm s$)

Groups	n		NO ($\mu\text{mol/L}$)	Endothelin-1 (ng/L)
Control group	79	Before treatment	46.32±7.45	58.26±7.53
		After treatment	82.54±6.38 ^b	50.41±7.33 ^b
Observation group	79	Before treatment	48.39±6.92	56.43±8.25
		After treatment	115.42±8.16 ^{ab}	41.05±6.23 ^{ab}

Note: Compared with control group, ^a $P<0.05$; Compared with before treatment, ^b $P<0.05$.

2.3 两组一般指标的比较

两组的心率、血压、肾功能、肝功能和血常规相比差异均无明显统计学意义 ($P>0.05$),且两组均无明显不良反应发生。

3 讨论

慢性心力衰竭是心血管内科常见疾病,呈慢性长期的进行性发展,5 年病死率达 50%^[9]。慢性心力衰竭的病因及发病机制较复杂,但目前临床普遍认为与心肌重塑、中枢神经系统和神经内分泌系统的过度激活有关^[9,10]。慢性心力衰竭是由炎症、心

表 3 两组一般指标的比较($\bar{x} \pm s$)

Table 3 Comparison of the general indicators between two groups before and after treatment

Groups	n		Heart rate(times /min)	Systolic pressure (mmHg)	Creatinine ($\mu\text{mol/L}$)	Alanine amino transférase (U/L)	Numeration of leukocyte ($\times 10^9/\text{L}$)
Control group	79	Before treatment	82.15 $\pm$ 5.32	135.15 $\pm$ 6.42	39.51 $\pm$ 6.22	37.55 $\pm$ 2.62	7.64 $\pm$ 2.33
		After treatment	80.34 $\pm$ 5.11	131.74 $\pm$ 5.21	42.54 $\pm$ 5.62	36.51 $\pm$ 2.15	7.22 $\pm$ 3.14
Observation group	79	Before treatment	83.20 $\pm$ 4.65	133.52 $\pm$ 4.24	41.27 $\pm$ 5.80	38.62 $\pm$ 2.37	7.55 $\pm$ 2.25
		After treatment	81.54 $\pm$ 4.97	134.32 $\pm$ 3.14	43.72 $\pm$ 7.91	35.44 $\pm$ 1.84	6.87 $\pm$ 1.56

心肌梗死等原因引起心肌结构和功能发生变化,最终导致心室泵血功能下降,是各种心脏疾病进展的最终结局,冠状动脉硬化、慢性肺疾病、风湿性心脏病、高血压等均可导致慢性心衰的发生,具有较高的发病率和死亡率^[1]。血管内皮与血液和血管组织直接接触,是血管损伤最直接的"靶点"^[12]。研究显示慢性心力衰竭的病理生理改变与内皮功能不全存在关联^[13-16]。曲美他嗪作为一种新型的优化心肌代谢、抗心肌缺血药物,是新型长链 3- 酮酰辅酶 A 硫解酶抑制剂,其与钙通道阻滞剂、 β - 受体阻滞剂、血管紧张素转化酶抑制剂有协同作用,可以明显增加心肌收缩力,改善心肌功能,增加心肌利用氧的能力,促进心肌葡萄糖的代谢,抑制体内炎性反应,减轻酸中毒,抑制游离脂肪酸的氧化,提高心肌细胞能量的产生^[17,18]。

血流介导血管舒张功能是评价机体内皮功能的重要指标,且因其利用超声检测,具有可行性和无创性的优点,在国内外应用广泛^[19-21]。Katz SD 等^[22]对 149 例慢性心力衰竭患者行经超声检测血流介导血管舒张功能,结果显示血流介导血管舒张功能的降低与心功能等级呈明显相关性。本研究采用血流介导血管舒张功能作为慢性心力衰竭的治疗指标之一,血管内皮舒张功能改善越明显,说明患者心功能越好,可间接体现治疗效果。本研究结果显示采用曲美他嗪治疗的患者治疗后的血流介导血管舒张功能明显高于治疗前,且肱动脉内径和血流介导血管舒张功能均明显高于常规治疗的患者,表明慢性心力衰竭患者的内皮依赖性血管舒张功能受到损伤,在抗心力衰竭常规治疗的基础上,曲美他嗪可以进一步改善内皮依赖性血管舒张功能,与国内外研究结果一致^[23,24]。

慢性心力衰竭患者体内内皮素 -1 水平升高可能与心输出量降低、组织缺氧及神经内分泌激活有关;同时内皮素 -1 又可直接激活多种细胞因子和激素,进而参与慢性心衰的病理生理过程^[25]。一氧化氮改善血管内皮功能的机制可能包括以下几方面^[26,27]:①拮抗血管收缩因子、调节血流介导血管舒张功能、降低血压、降低血管僵硬度,是血管紧张度、血流及血压的重要"调节器";②抑制三羟甲基氨基甲烷磷酸盐,诱导蛋白激酶 C 易位,降低钙超载,抑制中性粒细胞的损伤;③抑制血小板聚集、促进管修复及再生、抗感染、降低氧化应激的作用;④减轻再灌注损伤^[28,29]。本研究结果显示曲美他嗪治疗的患者治疗后的内皮素 -1 水平显著低于、一氧化氮显著高于常规治疗的患者,提示曲美他嗪可能通过降低血浆内皮素 -1 水平、升高一氧化氮水平改善慢性心力衰竭患者的血管内皮功能。在此研究基础上,为了进一步探讨曲美他嗪的用药安全性,我们分析了患

者治疗前后心率、血压、肾功能、肝功能和血常规的结果,结果显示所有患者以上指标变化差异不明显,且均无明显不良反应发生,表明曲美他嗪具有较高的安全性。

综上所述,曲美他嗪可显著改善慢性心力衰竭患者的血管内皮功能,可能与其降低血浆内皮素 -1 水平、升高一氧化氮水平有关。

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