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补肾活血汤联合卡托普利治疗老龄自发性高血压大鼠的机制研究*

彭金祥¹ 姜卫东¹ 陆晓晨² 高 想¹ 郑晓丹¹ 陈爱兰³ 张锋莉¹ 盛 炜¹

(1 南京中医药大学南通附属医院心血管病科 江苏 南通 226001;

2 南通大学附属医院心内科 江苏 南通 226001; 3 广州医科大学附属第一医院心血管内科 广东 广州 510120)

摘要 目的:探讨补肾活血汤联合卡托普利对老龄自发性高血压大鼠(SHR)的降压疗效并分析其作用机制。**方法:**选取 60 只 SHR 按照随机数字表法分为卡托普利组、补肾活血汤组、联合组、模型组,每组 15 只,另选取 15 只 Wistar-Kyoto 大鼠为空白组。联合组给予补肾活血汤联合卡托普利悬浊液灌胃干预,补肾活血汤组给予补肾活血汤灌胃干预,卡托普利组给予卡托普利悬浊液灌胃干预,模型组和空白组给予蒸馏水灌胃干预,连续干预 8 周。检测干预前、干预 4 周后、8 周后各组大鼠尾动脉收缩压,对比各组大鼠干预 8 周后血清炎症因子 C 反应蛋白(CRP)和肿瘤坏死因子- α (TNF- α)水平以及血清内皮素(ET)、血管紧张素 II(Ang II)、一氧化氮(NO)浓度。**结果:**干预前后,SHR 各组大鼠尾动脉收缩压高于空白组($P<0.05$),干预 4 周后、8 周后,联合组、补肾活血汤组、卡托普利组尾动脉收缩压均低于模型组,且联合组尾动脉收缩压低于卡托普利组、补肾活血汤组($P<0.05$);干预后补肾活血汤组与卡托普利组尾动脉收缩压比较差异无统计学意义($P>0.05$)。干预 8 周后,模型组、卡托普利组、补肾活血汤组 CRP、TNF- α 水平与空白组比较显著升高($P<0.05$),联合组 CRP、TNF- α 水平与空白组比较差异无统计学意义($P>0.05$),卡托普利组、补肾活血汤组、联合组 CRP、TNF- α 水平呈逐渐降低趋势,组间比较差异有统计学意义($P<0.05$)。干预 8 周后,模型组、卡托普利组、补肾活血汤组 ET、Ang II 浓度与空白组比较显著升高($P<0.05$),联合组 ET、Ang II 浓度与空白组比较差异无统计学意义($P>0.05$),联合组、补肾活血汤组、卡托普利组 ET、Ang II 浓度低于模型组,且联合组低于卡托普利组、补肾活血汤组($P<0.05$);模型组、卡托普利组 NO 浓度低于空白组、补肾活血汤组、联合组($P<0.05$),空白组、补肾活血汤组、联合组 NO 浓度比较差异无统计学意义($P>0.05$)。**结论:**补肾活血汤联合卡托普利对 SHR 有明显的降压作用,其机制可能与降低血清炎症因子、ET、Ang II 含量和升高 NO 含量有关。

关键词: 补肾活血汤;卡托普利;老龄;自发性高血压;大鼠;炎症因子;血管内皮功能

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Mechanism of Bushen Huoxue Decoction Combined with Captopril in the Treatment of Senile Spontaneously Hypertensive Rats*

PENG Jin-xiang¹, JIANG Wei-dong¹, LU Xiao-chen², GAO Xiang¹,

ZHENG Xiao-dan¹, CHEN Ai-lan³, ZHANG Feng-li¹, SHENG Wei¹

(1 Department of Cardiology, Nantong Affiliated Hospital of Nanjing University of Traditional Chinese Medicine, Nantong, Jiangsu, 226001, China; 2 Department of Cardiology, Affiliated Hospital of Nantong University, Nantong, Jiangsu, 226001, China;

3 Department of Cardiology, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, 510120, China)

ABSTRACT Objective: To investigate the antihypertensive effect of Bushen Huoxue Decoction Combined with captopril on senile spontaneously hypertensive rats (SHR) and to analyze its mechanism. **Methods:** 60 SHR were randomly divided into captopril group, Bushen Huoxue Decoction group, combined group and model group, with 15 rats in each group, 15 Wistar-Kyoto rats were selected as blank group. The combined group was treated with Bushen Huoxue Decoction Combined with captopril suspension, Bushen Huoxue Decoction group given Bushen Huoxue Decoction gavage intervention, the captopril group was given captopril suspension for gastric intervention, Model group and blank group were treated with distilled water for intragastric intervention, continuous intervention for 8 weeks. The systolic blood pressure of the tail arteries of the rats was measured before, 4 weeks and 8 weeks after intervention. The levels of serum inflammatory factors C reactive protein (CRP) and tumor necrosis factor- α (TNF- α), serum endothelin (ET), angiotensin II (Ang II) and nitrogen oxide (NO) were compared for 8 weeks after intervention. **Results:** Before and after the intervention, the systolic blood pressure of tail artery in each SHR group was higher than that in blank group ($P<0.05$). After 4 weeks and 8 weeks of intervention, the systolic blood pressure of tail artery in combined group, Bushen Huoxue Decoction group and captopril group was lower than that in model group, and the systolic blood pressure of tail artery in combined group was lower than that in captopril group and Bushen Huoxue Decoction group ($P<0.05$); after the intervention, the systolic blood pressure of tail artery in was no significant difference between

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作者简介: 彭金祥(1984-), 男, 硕士, 主治医师, 研究方向: 中西医结合心血管疾病, E-mail: ntzyypjx@163.com

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Bushen Huoxue Decoction group and captopril group ($P>0.05$). After 8 weeks of intervention, the levels of CRP and TNF- α in the model group, captopril group and Bushen Huoxue Decoction group were significantly higher than those in the blank group ($P<0.05$), there was no significant difference in the levels of CRP and TNF- α between the combined group and the blank group ($P>0.05$), and the levels of CRP and TNF- α in the captopril group, Bushen Huoxue Decoction group, combined group decreased gradually, and there was significant difference between the groups ($P<0.05$). After 8 weeks of intervention, the concentrations of ET and Ang II in the model group, captopril group and Bushen Huoxue Decoction group were significantly higher than those in the blank group ($P<0.05$), there was no significant difference in the concentrations of ET and Ang II between the combined group and the blank group ($P>0.05$). The concentrations of ET and Ang II in the combined group, Bushen Huoxue Decoction group and captopril group were lower than those in the model group, and the combined group was lower than those in the captopril group and Bushen Huoxue Decoction group ($P<0.05$). The concentrations of NO in model group and captopril group was lower than that in blank group, Bushen Huoxue Decoction group and combination group ($P<0.05$), and there was no significant difference in NO concentration among blank group, Bushen Huoxue Decoction group and combination group ($P>0.05$). **Conclusion:** Bushen Huoxue Decoction Combined with captopril has obvious antihypertensive effect on SHR, and its mechanism may be related to the decrease of serum inflammatory factors, ET, Ang II content and increasing NO content.

Key words: Bushen Huoxue Decoction; Captopril; Senile; Spontaneous hypertension; Rats; Inflammatory factors; Vascular endothelial function

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前言

自发性高血压是临床上一种较为常见的多发性遗传疾病,严重危害着人类的健康,随着人口老龄化的加剧,该病的患病率逐年增加,老年自发性高血压作为高血压中一种特殊类型,是引起老年人冠心病、心功能不全、肾衰等疾病的重要因素之一^[1-3]。近年来,中药由于毒副作用小、多靶点等优势已成为研究热点,补肾活血汤是由桑寄生、女贞子、淫羊藿、牛膝、丹参、黄芪、钩藤、益母草组成,具有多靶点降压的药理作用^[4,5]。相关研究显示^[6,7],炎症因子如C反应蛋白(C reaction protion, CRP)、肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)参与了高血压的病理生理过程,高血压患者血清中CRP、TNF- α 水平将显著高于正常人,且患者血压越高,血清中CRP、TNF- α 浓度也越高。另外,血管内皮功能障碍是自发性高血压的始动因素,同时也是导致靶器官受损的重要因素^[8]。血管内皮细胞主要是通过释放血管活性肽物质调节血压、调节血管张力,其中内皮素(endothelin, ET)、血管紧张素II(angiotensin II, Ang II)和一氧化氮(nitric oxide, NO)均参与动脉粥样硬化的发生与发展^[9,10]。当血管内皮受损时,活性肽物质分泌失衡,从而引发心血管疾病的发生。本次研究以老龄自发性高血压大鼠(spontaneously hypertensive rats, SHR)作为研究对象,探讨补肾活血汤联合卡托普利的降压作用,并通过比较大鼠炎症因子及血管内皮功能的变化,来分析补肾活血汤的降压机制,为补肾活血汤的临床应用提供理论基础。现将结果整理如下。

1 材料与方法

1.1 实验动物与分组

选取18月龄雄性SHR 60只,按照随机数字表法分为卡托普利组、补肾活血汤组、联合组、模型组,每组15只,另选取同月龄雄性Wistar-Kyoto大鼠15只作为空白组,其中卡托普利组大鼠体重203-249 g,平均(230.76 $\pm$ 26.16)g;补肾活血汤组大鼠体重205-251 g,平均(231.58 $\pm$ 25.84)g;联合组大鼠体重201-246 g,平均(235.61 $\pm$ 25.32)g;模型组大鼠体重207-253 g,

平均(236.22 $\pm$ 25.33)g;空白组大鼠体重206-250 g,平均(232.99 $\pm$ 24.31)g。各组大鼠体重比较差异无统计学意义($P>0.05$),24 $^{\circ}$ C-26 $^{\circ}$ C条件下恒温喂养,定时通风,换垫料,光照时间12 h,自由饮用自来水,基础饲料适应性喂养7 d。

1.2 实验药物及干预方法

补肾活血汤配制:桑寄生20 g;女贞子15 g;淫羊藿15 g;牛膝15 g;丹参10 g;黄芪10 g;钩藤(后人)15 g;益母草15 g,严格按照2015版《中国药典》的相关规定制备成0.63 g/mL浓度补肾活血汤液。卡托普利混悬液的配制:卡托普利片(开博通),中美上海施贵宝制药有限公司生产(国药准字H31022986),每片12.5 mg,研磨成粉,用蒸馏水溶解成3.5 mg/mL混悬液。所有实验大鼠均自由进食饮水,每天上午十点灌胃干预一次,由同一名研究人员操作,连续干预8周。具体方案如下,联合组:给予补肾活血汤10 mL/kg进行灌胃,联合给予卡托普利悬浊液10 mL/kg;补肾活血汤组:给予补肾活血汤10 mL/kg进行灌胃;卡托普利组:给予卡托普利混悬液10 mL/kg进行灌胃;模型组:给予蒸馏水10 mL/kg进行灌胃;空白组:给予蒸馏水10 mL/kg进行灌胃。

1.3 观察指标

采用RBP-1型大鼠尾压心率测定仪测定干预前、干预4周后、8周后尾动脉收缩压,具体方法为:先将大鼠放入保温套,温度为38.5 $^{\circ}$ C左右,大约10 min,大鼠尾动脉充分扩张后暴露大鼠尾巴,放入加压尾套,感应并测定尾动脉收缩压,连续测量三次,三次尾动脉收缩压的平均值即为尾动脉血压值。所有大鼠末次干预后禁食不禁水10 h,尾动脉采血10 mL,于30 min内超速离心取上清液,离心条件为:10 min,3500 r/min,采用酶联免疫吸附试验法检测血清CRP和TNF- α 水平,试剂盒购于德国Herrenberg公司,检测仪器为上海巴玖实业有限公司生产的DG5033A全自动酶免分析仪。采用放射免疫分析技术检测血清ET、Ang II及NO浓度,试剂盒购于德国Herrenberg公司,检测仪器为上海核所日环光电仪器有限公司生产的SN-6100型全自动放射免疫 γ 计数器,上述操作严格按照试剂盒说明进行。

1.4 统计学方法

采用 SPSS 25.0 进行数据分析, 计量资料以($\bar{x} \pm s$)的形式表示, 采用 t 检验分析, 计数资料以例数及百分率表示, 比较采用卡方检验, 以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 各组大鼠干预前后尾动脉血压变化比较

干预前后, SHR 各组大鼠尾动脉收缩压高于空白组 ($P < 0.05$), 干预 4 周后、8 周后, 联合组、补肾活血汤组、卡托普利组尾动脉收缩压均低于模型组, 且联合组尾动脉收缩压低于卡托普利组、补肾活血汤组 ($P < 0.05$), 干预后补肾活血汤组与卡托普利组尾动脉收缩压比较差异无统计学意义 ($P > 0.05$)。见表 1。

表 1 各组大鼠干预前后尾动脉收缩压变化比较($\bar{x} \pm s$)

Table 1 Comparison of the changes of systolic blood pressure of tail artery in each group before and after intervention($\bar{x} \pm s$)

Groups	n	Before intervention(mmHg)	4 weeks after intervention (mmHg)	8 weeks after intervention (mmHg)
Combined group	15	175.45±10.22 ^a	136.02±10.75 ^{abcd}	134.40±10.71 ^{abcd}
Bushen Huoxue Decoction group	15	175.52±9.98 ^a	159.98±10.50 ^{ab}	156.85±10.44 ^{ab}
Captopril group	15	174.27±10.12 ^a	158.73±10.46 ^{ab}	154.84±10.35 ^{ab}
Model group	15	174.16±10.28 ^a	175.62±11.06 ^a	174.03±11.16 ^a
Blank group	15	115.07±10.01	116.14±9.82	115.90±9.86

Note: compared with blank group, ^a $P < 0.05$; compared with model group, ^b $P < 0.05$; compared with captopril group, ^c $P < 0.05$; compared with Bushen Huoxue Decoction group, ^d $P < 0.05$.

2.2 各组大鼠干预 8 周后血清炎症因子比较

干预 8 周后, 模型组、卡托普利组、补肾活血汤组 CRP、TNF- α 水平与空白组比较显著升高 ($P < 0.05$), 联合组 CRP、

TNF- α 水平与空白组比较差异无统计学意义 ($P > 0.05$), 卡托普利组、补肾活血汤组、联合组 CRP、TNF- α 水平呈逐渐降低趋势, 组间比较差异有统计学意义 ($P < 0.05$)。见表 2。

表 2 各组大鼠干预 8 周后血清炎症因子比较($\bar{x} \pm s$)

Table 2 Comparison of serum inflammatory factors of rats in each group after 8 weeks of intervention($\bar{x} \pm s$)

Groups	n	CRP(mg/L)	TNF- α (mg/mL)
Combined group	15	21.15±1.17 ^{bcd}	33.09±2.74 ^{bcd}
Bushen Huoxue Decoction group	15	25.54±1.09 ^{abc}	36.32±2.87 ^{abc}
Captopril group	15	33.09±1.27 ^{ab}	41.51±2.96 ^{ab}
Model group	15	36.18±1.45 ^a	54.84±3.52 ^a
Blank group	15	20.12±1.21	32.39±3.18

Note: compared with blank group, ^a $P < 0.05$; compared with model group, ^b $P < 0.05$; compared with captopril group, ^c $P < 0.05$; compared with Bushen Huoxue Decoction group, ^d $P < 0.05$.

2.3 各组大鼠干预 8 周后血管内皮功能比较

干预 8 周后, 模型组、卡托普利组、补肾活血汤组 ET、Ang II 浓度与空白组比较显著升高 ($P < 0.05$), 联合组 ET、Ang II 浓度与空白组比较差异无统计学意义 ($P > 0.05$), 联合组、补肾活血汤组、卡托普利组 ET、Ang II 浓度低于模型组, 且联合组低于

卡托普利组、补肾活血汤组 ($P < 0.05$), 模型组、卡托普利组 NO 浓度低于空白组、补肾活血汤组、联合组 ($P < 0.05$), 空白组、补肾活血汤组、联合组 NO 浓度比较差异无统计学意义 ($P > 0.05$)。见表 3。

表 3 各组大鼠干预 8 周后血管内皮功能比较($\bar{x} \pm s$)

Table 3 Comparison of vascular endothelial function of rats in each group after 8 weeks of intervention($\bar{x} \pm s$)

Groups	n	ET(pg/mL)	Ang II (pg/mL)	NO(μ mol/mL)
Combined group	15	92.65±25.65 ^{bcd}	125.48±16.07 ^{bcd}	165.62±20.06 ^{bc}
Bushen Huoxue Decoction group	15	135.24±27.58 ^{ab}	130.58±17.65 ^{abc}	164.32±20.11 ^{bc}
Captopril group	15	140.16±31.34 ^{ab}	140.23±19.46 ^{ab}	132.49±19.09 ^a
Model group	15	185.14±35.32 ^a	169.98±21.11 ^a	130.51±20.08 ^a
Blank group	15	87.93±23.30	110.93±22.14	165.53±20.12

Note: compared with blank group, ^a $P < 0.05$; compared with model group, ^b $P < 0.05$; compared with captopril group, ^c $P < 0.05$; compared with Bushen Huoxue Decoction group, ^d $P < 0.05$.

3 讨论

自发性高血压是老年人常见的一种心血管疾病, 据统计, 我国 60 岁及以上老年人高血压的患病率高达 49%, 随着近年来人口老龄化的加剧, 预计到 2050 年, 高血压的患病率还将继续增加^[11,12], 另外, 高血压还会引发脑卒中、冠心病、心衰等一系列的心脑血管疾病, 严重危害老年人身体健康, 影响老年人生生活质量^[13]。因此尽早诊断、及时治疗对自发性高血压病情控制显得尤为重要。近年来, 中药在治疗老年自发性高血压方面取得突破性进展, 其优势在于疗效稳定、在改善患者病情的同时能保护靶器官, 减少并发症^[14,15]。中医学认为肾虚血瘀是老年自发性高血压发生发展的重要病理机制^[16,17], 补肾活血、化瘀通络是治疗该病的关键, 补肾活血汤是由桑寄生、女贞子、淫羊藿、牛膝、丹参、黄芪、钩藤、益母草八味中药组成, 桑寄生有补肝肾、强筋骨之功效, 女贞子有补肾养阴、乌须明目之功效, 淫羊藿有补肾壮阳之功效, 牛膝有祛瘀血、通血脉之功效, 丹参有活血凉血之功效, 黄芪有补气健脾之功效, 钩藤有清热平肝、熄风止痉之功效, 益母草有活血调经、利水消肿之功效, 诸药合用发挥补肾活血的作用^[18-20]。

本研究结果显示, 干预前, SHR 各组大鼠尾动脉收缩压高于空白组, 表明研究模型制备成功。卡托普利为人工合成的非肽类血管紧张素转化酶抑制剂, 用于治疗各种类型的高血压, 是临床医生治疗高血压的首选药物, 此外它还可以改善心肌损伤^[21,22], 本研究结果显示干预 8 周后, 补肾活血汤与卡托普利联合应用降压作用明显, 且显著优于单独使用卡托普利和单独使用补肾活血汤。越来越多的研究显示炎症因子参与高血压的发生发展, 炎症因子与高血压互相影响, 互为因果, 形成恶性循环, 一方面, 炎症因子可以通过刺激血管, 使得舒血管物质与缩血管物质的分泌平衡被打破, 从而引起血压升高^[23,24]; 另一方面, 高血压会导致血管内皮受损, 血压血流冲击动脉壁引发损伤^[25,26], 并引发主动脉管壁增厚以及动脉粥样硬化, 从而刺激血管内皮分泌炎症因子, 致使患者血清炎症因子升高, 其中 CRP、TNF- α 是炎症反应的敏感指标^[27,28]。本研究结果显示补肾活血汤与卡托普利联合应用可以显著改善高血压大鼠的炎症反应, 且作用明显优于单独使用卡托普利和单独使用补肾活血汤。

近年来有研究显示^[29,30], 血管内皮功能异常也参与高血压的发生发展, 内皮功能异常导致内皮依赖性舒张血管减弱, 并通过分泌 NO、ET、Ang II 来调节血管张力, 控制血压。NO 是一种舒血管物质, 它通过激活鸟苷酸环化酶来升高细胞内环磷鸟苷水平, 减少 Ca^{2+} 浓度, 舒张血管, 但是当高血压出现时, NO 的分泌会减少。另外 NO 还具有抑制肾素合成、抑制血小板聚集等作用, 保障血液流通及降压。ET 则是体内血管收缩因子, 抑制 ET 的分泌可以起到保护血管的作用。ET 与 NO 作用相反, 两者在机体内保持平衡, 维持正常血压及血液循环。Ang II 是肾素-血管紧张素系统中的最重要的物质, 当其浓度升高时, 与血管紧张素受体结合, 引起血管收缩血压升高。本研究结果表明, 干预 8 周后, 联合组 ET、Ang II、NO 浓度与空白组无明显差异, 且联合组 ET、Ang II 浓度低于补肾活血汤组、卡托普利组、模型组, NO 浓度高于卡托普利组、模型组, 提示补肾活血汤与卡托普利联合应用可以显著降低血清 ET、Ang II 浓度, 升

高血压 NO 浓度, 通过调节血管的舒缩, 来降低血压。

综上所述, 补肾活血汤与卡托普利联合应用可以显著降低老年 SHR 血压, 其作用机制可能通过降低炎症因子 CRP、TNF- α 水平, 改善血管内皮功能, 降低血清 ET、Ang II 浓度, 升高血清 NO 浓度来实现的。

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