·实验研究·

中医阴阳的实验性研究(IV)

附子、肉桂和六味地黄方对肾血管性高血压大鼠心肌的作用

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内容提要 实验证实二肾一夹型高血压大鼠心肌肥厚伴有左室壁羟脯氨酸浓度明显增加，并发现助阳药附子加剧这种改变，而滋阴药六味地黄方则减轻这种改变。六味地黄方降低心肌羟脯氨酸浓度，间接提示减少心肌胶原的沉着作用，这可能为该方防治心血管损害提供一定依据。由助阳药和滋阴药对该模型羟脯氨酸浓度的相反作用，可推想二肾一夹型高血压可能为中医的"阴虚"模型。

慢性高血压引起心脏和血管壁肥厚及硬化，成为各种并发症的病理基础。在以前的研究中[1]，曾发现助阳药附子、肉桂在二肾一夹肾血管性高血压大鼠使血压显著升高，传统的滋阴药方"六味地黄"则不改变血压水平。为了深入弄清楚附子，肉桂或六味地黄分别对高血压性心血管损害的影响如何，选取了心脏重量指数和心肌羟脯氨酸浓度两个指标反映心脏肥厚及硬化程度。测定心肌中羟脯氨酸浓度估计胶原形成与沉积的多寡，比较给药前后的变化，并对其机制作初步探讨。

材料和方法

实验用 Wistar 大鼠，雌雄不拘，体重 150～250g。用固定配方的颗粒饲料和普通饮水喂养，置 24°C 左右环境中。在戊巴比妥钠腹腔麻醉下，用 0.2mm 内径银夹狭窄左肾动脉，右肾不触及。用尾容积法每周测量大鼠清醒状态下收缩压(SBP)一次。每周称体重一次。收缩压高于术前 20mmHg，并大于 120mmHg 者确立为高血压大鼠。术后六周，把高血压大鼠分为对照、附子＋肉桂(附桂)、附子单味和六味地黄(地黄、山茱萸、山药、泽泻、牡丹皮和茯苓)等组。用药物水煎浓缩液灌胃，每天一次，剂量按体重计为成人量 10 倍，疗程为四周。另设不手术大鼠为正常组。

灌胃四周后，即术后十周末，断头处死所有大鼠。取出完整心脏，剪开，用生理盐水冲洗净，吸干并于精细天平上称取湿重。计算心脏重量指数：心脏湿重(mg)/体重(g)。然后用丙酮—乙醚混合液脱脂 24 小时，2 次。在 105°C 烘箱内干燥至恒重，再称取干重。精确称取干燥心脏样品的左室壁组织 10mg 置于安瓿内，加 1 ml 6N盐酸，在 110°C 下水解 8 小时以上。经中和后用对—二甲氨基苯甲醛显色法测定羟脯氨酸含量[2]，并计算左室壁羟脯氨酸浓度（μg/mg 组织)。

结 果

给药或水前，高血压对照、六味地黄、附子和附桂组的收缩血压(M±SE，以下同）分别为 148.0±2.8、148.0±1.8、144.0±3.3 和 142.0±2.9mmHg，组间血压无显著差异。手术后第六周始灌药或水，灌胃四周后，对照和六味地黄组血压分别为 146.±3.4 和 146.0±2.1mmHg，无明显改变 (P＞0.05)；附子和附桂组血压分别为 158.0±2.5和157.0±3.0mmHg，比给药前明显升高(P＜0.01)；正常血压组大鼠血压无明显变化。各组大鼠生长曲线正常。

各组大鼠心脏重量指数与左室壁羟脯氨酸浓度见附表。

二肾一夹肾血管性高血压组大鼠重量指数增大，为正常血压组大鼠的128%，与收缩血压显著相关(r＝0.643)；心肌羟脯氨酸浓度升高，为正常组的 165%，与收缩血压也显著相关 (r＝0.516)。发现附子组比高血压对照组有较高的左室壁羟脯氨酸浓度(P＜0.01)，上升 18.1%；六味地黄组则相反，羟脯氨酸浓度虽然

高于正常组，低于对照组($P<0.01$)，下降 25.1%；附桂组与对照组之间无显著差异($P>0.05$)。心脏重量指数，六味地黄、附子、附桂与对照组之间未显示有显著差异。

附表　附子等对肾血管性高血压大鼠心脏的作用(M±SE)

组　别(n)	心脏重量指数 (mg/g)	左室壁羟脯氨酸 (μg/mg)	
正　　常(10)	2.93±0.08	2.41±0.16	
高血压对照(17)	3.75±0.17	3.98±0.32△△	↑
六味地黄(13)	3.57±0.16	2.98±0.28**	↓
附　　子(14)	3.80±0.24	4.70±0.54*	↑
附　　桂(15)	3.86±0.23	3.83±0.29	

正常组——高血压对照　△△$P<0.01$　↑增高
给药组——高血压对照　*　$P<0.05$　↓减低
　　**　$P<0.01$

讨　论

高血压性心脏肥厚是心脏对压力后负荷升高的一种适应性结构改变，发生心肌细胞肥大，纤维结缔组织增生以及冠状血管床增加。心脏肥厚时有一系列的生化变化，在早期 RNA 浓度增加，DNA 依赖的 RNA 聚合酶活性上升，肌球蛋白合成增加。随着过度而持久的压力负荷继续存在或加强，合成 RNA 和肌球蛋白等的能力逐渐下降乃至耗竭。然而羟脯氨酸浓度与含量（反映胶原沉着）在心脏肥厚的整个过程持续增加，引起心脏左室顺应性降低[3]。本文结果证实在二肾一夹肾血管性高血压大鼠心脏肥厚时有左室壁羟脯氨酸浓度的显著增加，并发现助阳药附子加剧这种改变，而滋阴药六味地黄方则减轻之。“助阳”、“滋阴”不同属性的传统中药，对同一高血压疾病模型心肌羟脯氨酸呈相反的作用，是值得注意的启示。我们在二肾一夹高血压模型已发现附子和六味地黄对脑干、下虚脑和纹状体的脑啡肽含量有相反作用而推想此为阴虚模型[4]。本实验的发现有助于向此方向推想，在动物模型中具有重要意义。

附子等药物却并不显著改变心脏重量指数，这可能是高血压肥厚发生发展要有适当的时间过程，也许本实验的疗程不够，心肌肥厚的变化尚未明显反映出来。附子与六味地黄方对心肌羟脯氨酸浓度相反效应的机理，从本文尚难以获得阐明。有人认为除压力负荷外，神经和激素因素也是高血压性心脏肥厚的原因，包括反复增强的交感激惹反应。Yamari[5] 发现静脉滴注异丙基肾上腺素时，虽然血压并不升高，大鼠可发生明显的心脏肥厚。有研究报道[6]，附子可能具有拟肾上腺素样活性，这或许与附子升高心肌羟脯氨酸浓度有关。滋阴六味地黄方的药理作用较广泛，本研究发现它具有减少心肌胶原沉着的作用，这为六味地黄汤防治高血压病心血管等损害提供了一定的依据。

通过本研究工作，有几点粗略的印象，二肾一夹肾血管性高血压模型可能是阴虚模型。并且由于六味地黄汤是传统的滋补肾阴的名方，于该模型有某些治疗效果，因而进一步推想本疾病模型为肾阴虚模型是可能的；六味地黄汤减少胶原沉着，因而以实验性模型说明本方可能对心血管病有治疗指征，可能产生一定的治疗效果；二十年来我们用动物疾病模型来探索中医的阴阳学说（如考的松阳虚证模型、高血压疾病模型等），看来有一定的理论价值，研究的结果对临床实践也可能产生积极的启发作用。

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江苏省中医多学科学术讨论会在南京召开

1984年 11 月 21～24 日在南京市召开了江苏省中医多学科研究学术讨论会，与会代表 130 余人，收到论文 86 篇，论文及会议报告的内容涉及中医理论、中西医结合、医学史以及天文、地理、心理、物理化学、文史考古等多种学科对中医的阐述和研究，为中医现代化和研究人与自然的关系提供了新的资料。

（林祖虞）

45 Cases of Latent Glomerulonephritis Treated with TCM-WM

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A series of 45 cases of latent glomerulonephritis (totally 74 admissions in 13 years) were treated with TCM-WM. (1) 6 cases with albuminuria, hematuria and casts in the urine were treated with penicillin and modified Zhi Bai Di Huang Tang (知柏地黄汤). There are satisfactory symptoms remission in 4 cases and partial remission in 2 cases. (2) 4 cases with simple albuminuria (totally 6 admissions) were treated by using prednisone, cyclophosphamide (or Thio-TEPA) and modified Liu Wei Di Huang Tang (六味地黄汤), all with satisfactory remission. (3) 35 cases mainly with hematuria and casts in urine (totally 62 admissions) were treated alternatively with penicillin, erythromycin or gentamycin and with TCM simultaneously according to patients' symptoms and signs by using Liang Xue Zhi Xue (凉血止血), Zi Yin Zhi Xue (滋阴止血), Yi Qi Zhi Xue (益气止血), Wen Jing Zhi Xue (温经止血), Hua Yu Zhi Xue (化瘀止血), totally with satisfactory remission in 23 admissions, partial remission in 21 admissions, symptoms improved 12 admissions and treatment failure in 6 admissions. The final outcome of TCM-WM treatment for latent glomerulonephritis was good in 92% of the cases. (Original article on page 161)

The Effect of *Tripterygium Wilfordii* on the Remission of Albuminuria in Patients with Nephrotic Syndrome

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Thirty-seven cases with primary nephrotic syndrome treated with TCM-WM are reported, with emphasis on the effect of *Tripterygium wilfordii* on the remission of albuminuria. Shortly after the treatment with *Tripterygium wilfordii*, marked effect was observed in 5 of 10 cases of primary glomerulonephropathy, and moderate effect in the remaining 5 cases. Of the 20 cases of chronic glomerulonephritis, 7 showed significant effect, 12 showed moderate effect, only 1 case failed.

The average number of days needed for complete remission of albuminuria was 12.45 ± 4.74 (mean $\pm$ SD) in 11 of 25 cases of the lst group (treated with *Tripterygium wilfordii*); 10.63 ± 3.24 in 8 of 12 cases of the 2nd group (treated with *Tripterygium wilfordii* and prednisone) and 17.43 ± 8.48 in 7 of 13 cases of the 3rd group (treated with prednisone exclusively). Albuminuria in the lst and 2nd group disappeared more rapidly than in the 3rd group ($P < 0.02$). No significant difference was found between the lst and the 2nd group. It is suggested that preparations of *Tripterygium wilfordii* be used as substitute of corticosteroids. (Original article on page 164)

Experimental Research of Yin-Yang theory in TCM (IV)
Effect of Mankshood, Bark of Chincse Cassia Tree and Liu Wei Di Huang Fang on Myocardium of Renovascular Hypertensive Rats

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This study confirmed cardiac hypertrophy of the two-kidney one-clip Goldblatt hypertensive rats with high hydroxyproline level in the left ventricular wall. we found that mankshood of Yang-tonifying drug further increased the hydroxyproline level while Liu Wei Di Huang Fang (Prescription of Six Drugs with Rehmannia: Radix Rehmanniae, Praeparata Fructus Corni, Rhizoma Discoreae, Cortex Moutan Radicis, Rhizoma Alismatis and Poria) of Yin-nourishing drug decreased its level. Mankshood was found to act on cardiac hypertrophy like adrenaline, which might be explained by its ability to elevate myocardial hydroxyproline level. However, Liu Wei Di Huang Fang decreased myocardial hydroxyproline content, and thus indirectly reduced the deposition of myocardial collagen. Therefore, Liu Wei Di Huang Fang might serve as a means to prevent and treat cardiovascular lesions caused by hypertension.

We have demonstrated in this and the precedent paper that in the renovascular hypertensive rats, the action of drug Yang (mankshood root) and that of the drug Yin (Liu Wei Di Huang Fang) have an opposite effect on cardiac hydroxyproline and brain tissue enkephalin level, the drug Yang having a deteriorative while drug Yin a beneficial effect. The drug Yang elevated the hydroxyproline and lowered the enkephaline level. The drug Yin lowered the hydroxyproline and elevated the enkephaline level. These results suggested that these renovascular hypertensive rats model might serve as a Yin Xu model (Yin deficiency model).

This finding confirms our previous belief that drug Yang and drug Yin, by their opposite effect, can determine whether an experimental model is Yang Xu (Yang deficiency) or Yin Xu (Yin deficiency). It might also be applied to human diseases. (Original article on page 167)