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• 实验研究 •

硝苯地平 and 依那普利对兔 髂动脉球囊损伤后胶原增生的影响

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[关键词] 胶原; 再狭窄; 血管成形术; 血管紧张素转换酶抑制剂; 兔

[摘要] 为观察硝苯地平 and 依那普利对兔髂动脉血管成形术后胶原增生的作用, 将 32 只雄性新西兰大白兔随机分为对照组、硝苯地平组和依那普利组, 行右髂总动脉血管成形术。硝苯地平组和依那普利组于术前一天分别从耳静脉注射硝苯地平 100 ng/g 和依那普利 0.4 μg/g, 每 12 h 一次, 至术后两周。分别测定术前、术后 30 min 及术后两周血浆血管紧张素 Ⅱ含量, 行 Masson's 三色染色并进行图像分析。结果发现, 对照组术后 30 min 血管紧张素 Ⅱ含量由 2.70 ± 0.31 g/L 升高为 2.83 ± 0.18 g/L ($P < 0.05$), 两周后恢复至术前水平 (2.50 ± 0.26 g/L, $P > 0.05$); 硝苯地平组血管紧张素 Ⅱ含量与对照组无明显差异。依那普利组术后 30 min 血管紧张素 Ⅱ含量为 2.50 ± 0.09 g/L, 较术前 (2.57 ± 0.10 g/L) 无升高 ($P > 0.05$)。图像分析胶原含量表明, 血管损伤后两周血管壁胶原含量增高, 面密度、平均光密度及积分光密度明显增高 ($P < 0.01$); 依那普利组面密度、平均光密度及积分光密度显著低于对照组 ($P < 0.01$)。结果提示, 血管成形术后血管壁发生明显的胶原增生, 依那普利抑制血管壁胶原增生, 可能对预防经皮腔内冠状动脉成形术后再狭窄有效。

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The Effects of Nifedipine and Enalaprilat on Collagen Proliferation after Balloon Injury in a Rabbit Model

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MeSH Collagen; Restenosis; Angioplasty; Angiotensin Converting Enzyme Inhibitors; Rabbits

ABSTRACT **Aim** To evaluate the effectiveness of nifedipine and enalaprilat on collagen proliferation after balloon injury in a rabbit model. **Methods** Thirty- two healthy male New Zealand white rabbits were divided into control group, nifedipine group and enalaprilat group. Conventional balloon angioplasty in the right common iliac artery was done. Arterial bloods were taken before angioplasty, 30 minutes and 2 weeks after angioplasty for analyzing plasma Ang Ⅱ. For histology, Masson's staining was performed two weeks later. All the specimens were analyzed using a computerized imaging analysis system. **Results** In the control group, plasma Ang Ⅱ elevated from 2.70 ± 0.31 g/L to 2.83 ± 0.18 g/L 30 min after angioplasty ($P < 0.05$), and returned to 2.50 ± 0.26 g/L two weeks later ($P < 0.05$). There was no significant Ang Ⅱ differences between the control and the nifedipine groups. Enalaprilat significantly inhibited plasma Ang Ⅱ elevation 30 min after angioplasty. Histological computerized imaging analysis showed significant collagen proliferation after angioplasty ($P < 0.01$). There was a significant decrease of collagen proliferation in the enalaprilat group ($P < 0.01$). **Conclusions** Significant vascular wall collagen proliferation was observed after angioplasty. Enalaprilat inhibited vascular wall collagen proliferation, thus may be effective in the prevention of restenosis after successful percutaneous transluminal coronary angioplasty.

经皮腔内冠状动脉成形术后再狭窄的发生率约 30%, 其特征是细胞外基质和血管平滑肌细胞增殖。

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Schwartz 等^[1]研究表明人再狭窄组织细胞成分仅占新生内膜的 11%, 其余由细胞外基质构成。Violaris 等^[2]证实人再狭窄组织较粥样硬化组织含更多的胶原, 表明细胞外基质合成在再狭窄发生中起主要作用。本研究目的是观察钙离子拮抗剂硝苯地平 and 血管紧张素转换酶抑制剂依那普利对兔髂动脉血管成

形术后胶原增生的影响,评价其临床预防经皮腔内冠状动脉成形术后再狭窄的可行性。

1 材料和方法

1.1 动物模型制作

32只雄性新西兰大白兔,体重2.7~3.4 kg,随机分为对照组($n=16$)、硝苯地平组($n=8$)和依那普利组($n=8$)。用2.5 mm冠状动脉球囊扩张损伤右髂总动脉,术中0.1 IU/g肝素抗凝^[3]。手术前后普通兔饲料喂养两周。

1.2 实验组处理

硝苯地平组和依那普利组分别于血管成形术前一天从耳静脉注射硝苯地平100 ng/g、依那普利拉0.4 μg/g(由上海医药工业研究所合成室惠赠),每12 h一次,至术后两周。

1.3 病理标本制作

术后两周用10%中性福尔马林动脉恒压(80~90 mmHg)灌注15 min,分离双侧髂总动脉,从起始部起各取1 cm,平均切成四段,行HE及Masson's三色染色。用计算机辅助图象分析仪测定胶原的面密度、平均光密度和积分光密度。

1.4 血管紧张素Ⅱ含量测定

于血管损伤术前、术后30 min及术后两周动脉采血,用放射免疫法测定血管紧张素Ⅱ含量。

1.5 统计学分析

数据以 $\bar{x} \pm s$ 表示,各组间差异比较采用方差分析, $P < 0.05$ 表示相差显著, $P < 0.01$ 表示相差非常显著。

2 结果

2.1 血管紧张素Ⅱ含量变化

由表1(Table 1)可知,对照组术后30 min血管紧张素Ⅱ含量升高($P < 0.05$),术后两周恢复至术前水平;硝苯地平组术后30 min血管紧张素Ⅱ含量升高,与对照组无明显差异;依那普利组术后30 min血管紧张素Ⅱ含量较对照组明显降低($P < 0.01$)。

2.2 胶原含量测定

光镜下见损伤侧血管均显示弥漫性内膜增生,Masson's三色染色见胶原纤维呈蓝色,胞核呈黑色,胞浆、肌肉呈红色,胶原增生明显。图像分析测定胶原含量表明,对照组血管损伤后两周血管壁胶原含量增高,依那普利抑制术后胶原增生($P < 0.01$),见表2(Table 2)。

表1. 兔血管成形术前后血浆血管紧张素Ⅱ含量的变化。

Table 1. The changes of plasma Ang Ⅱ concentration During angioplasty in rabbits ($\bar{x} \pm s$, g/L).

Groups	n	Before	After 30 min	After 2 weeks
Control	16	2.70 ± 0.31	2.83 ± 0.18 ^a	2.50 ± 0.26
Enalaprilat	8	2.57 ± 0.10	2.50 ± 0.09 ^b	2.64 ± 0.22
Nifedipine	8	2.63 ± 0.18	2.80 ± 0.13 ^a	2.62 ± 0.14

a: $P < 0.05$, compared in the same group; b: $P < 0.01$, compared with control group.

表2. 兔血管成形术后两周胶原含量测定。

Table 2. Collagen measurement of the rabbit common iliac artery two weeks after angioplasty ($\bar{x} \pm s$, $10^3/m^2$).

Groups	Area density	Average OD	Intergal OD
Non- angioplasty	0.03 ± 0.01	0.05 ± 0.01	62.33 ± 24.5
Angioplasty	0.06 ± 0.02 ^a	0.09 ± 0.03 ^a	157.08 ± 49.18 ^a
Nifedipine	0.0 ± 0.01	0.08 ± 0.02	139.57 ± 36.24
Enalaprilat	0.04 ± 0.01 ^b	0.06 ± 0.02 ^b	103.88 ± 29.02 ^b

a: $P < 0.01$, compared with non- angioplasty group; b: $P < 0.01$, compared with angioplasty group.

3 讨论

经皮腔内冠状动脉成形术后,血管平滑肌细胞从中膜向内膜迁移,由收缩型向合成型转变,合成胶原蛋白的量增加25~30倍,在血管修复晚期以I型胶原为主,增大局部血管张力是再狭窄的因素之一^[4]。Strauss等^[5]对兔髂动脉再狭窄模型的研究表明,在术后4周内显著的胶原纤维增生,术后8周胶原和细胞外基质的合成下降。血管损伤后血管壁细胞外基质沉积还受损伤处释放的生长因子影响,转化生长因子可使正常血管细胞外基质合成增加,并伴有内膜和中膜增生,前胶原及胶原合成增多^[6],西拉普利和硝苯地平可使转移生长因子 β_1 基因表达减弱,血管壁细胞外基质沉积减少^[7]。本实验观察到血管损伤后30 min,血浆血管紧张素Ⅱ含量升高,术后两周恢复至术前水平。血管成形术后,不仅激活了循环肾素-血管紧张素系统,而且也激活了局部肾素-血管紧张素系统,使局部血管壁血管紧张素Ⅱ含量升高^[8]。血管紧张素Ⅱ可以使血管平滑肌细胞分泌转移生长因子 β 增加^[9],而且对产生细胞外基质蛋白有直接刺激作用^[10]。依那普利能抑制血管紧张素Ⅱ的产生,其抑制胶原增生的作用与血管紧张素Ⅱ、转移生长因子 β 的减少有关,可能对临床预防经皮腔内冠状动脉成形术后再狭窄有效。血管紧张素Ⅱ通过增加细胞内钙离子的浓度,使血

管平滑肌细胞和成纤维细胞增殖, 钙离子拮抗剂降低细胞内游离钙离子浓度, 抑制血管紧张素 E_2 的促增殖作用^[11]。有研究证实尼群地平可使高血压大鼠心肌胶原含量下降^[12], 维拉帕米可使血管平滑肌细胞胶原合成减少。本实验虽观察到硝苯地平组胶原含量减少, 但与对照组无统计学差异($P > 0.05$), 其临床意义有待进一步研究。

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