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尼可地尔对缺血区冠脉循环的作用

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Effect of nicorandil on coronary circulation in ischemic region

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ABSTRACT To clarify the role of nicorandil (Nic) in relieving myocardial ischemia, the effects of Nic in canine models of coronary arterial stenosis were studied. During stenosis of the anterior descending coronary artery by an external micrometer constrictor, intracoronary infusion of Nic 1, 5 μg / (kg · min) increased coronary blood flow and decreased distal coronary pressure, total coronary arterial resistance and small coronary arterial resistance; but did not affect mean aortic pressure, heart rate and large coronary arterial resistance. Whole blood viscosity, plasma viscosity and hematocrit in coronary vein after intracoronary infusion of Nic were reduced. The results of intravenous infusion of Nic were similar to those of intracoronary infusion.

These results indicate that Nic is capable of increasing coronary blood flow, alleviating myocardial ischemia due to direct dilatation of coronary artery and reduction of blood viscosity in ischemic region.

KEY WORDS nicorandil; coronary circulation; hemodynamics; rheology; myocardium; ischemia

提要 本文在实验性冠脉狭窄犬上, 观察到冠脉内恒流灌注尼可地尔(Nic 1, 5μg / kg · min)后, 冠脉流量增加. 远端小动脉压、冠脉血管总阻力和小冠脉血管阻力减低; 而血压和心率无明显改变. 冠状静脉的全血粘度、血浆粘度和血细胞比容降低. 股 iv 也得到相同的结果. 表明 Nic 有扩张缺血区冠脉和降低血液粘度的双重作用.

关键词 尼可地尔; 冠脉动脉循环; 血液动力学; 血液流变学; 心肌; 缺血

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冠状动脉硬化所致的狭窄可以引起心肌缺血等一系列改变, 使用扩血管药物可以纠正或缓解之.尼可地尔(nicorandil,Nic)是近年来发展起来的一种抗心绞痛新药, 它能扩张冠脉, 增加血流量[1], 改善缺血区心肌代谢和心脏功能[2], 增加心外膜流向心内膜的血流量[3]等. 目前尚不清楚的是; 1) Nic 改善心肌缺血是通过全身体循环作用还是直接作用于冠脉? 2) Nic 对缺血区冠脉是否有扩张作用? 其作用部位如何? 3) Nic 是否能改善缺血区血液流变学?为此, 本文在实验性冠脉狭窄犬上, 观察 Nic 对冠脉循环的上述作用, 并探讨了它在心肌缺血时作用的机理.

MATERIAL AND METHODS

Nic 由陕西省医药科研试验厂提供. 健康杂种犬 18 条, 体重 19 ± SD 4 kg, ♀♂不拘, 戊巴比妥钠 iv 麻醉开胸[4-6]后, 在冠脉左前降支第一分支下方安放电磁流量计 (MF-27) 探

头，测冠脉每分平均血流量(CBF)．探头后放一自制的微米缩窄器造成冠脉临界狭窄[4-6]．在冠脉狭窄上方和下方远端小动脉上分别逆行插管测主动脉平均压(MAP)，在行狭窄上方给药，测远端小动脉平均压(DCP)和行狭窄下方给药(Fig 1)． 分离右侧股静脉后，插管，用于iv． 犬接标准Ⅱ导联心电图以记录心率(HR)． 以上流量、压力、心电信号均输入多导记录仪 (Mingograf-800) 同步记录．

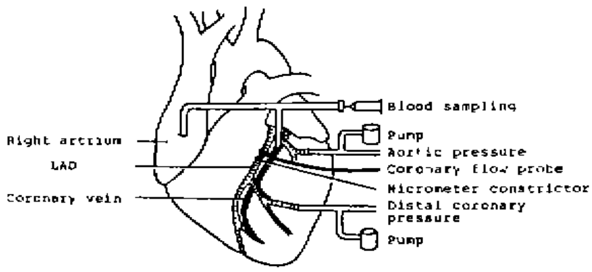

Fig 1. Cardiac preparation in studies on coronary artery stenosis.

冠状静脉取血法　在左前降支第一分支处分离伴行的冠状静脉，行冠状静脉-右心房回流术．即结扎冠状静脉远端，于近端插入一直径为 2 mm 事先经肝素处理的 Y 型硅胶管，一端插入右心房，另一端与采血器相接以收集局部静脉血样(Fig 1)．采血时，夹闭通向右心房的胶管，以防右心房血回流；在不采血时，冠状静脉血可以保持正常回流入右心房． 采血是在用药前和用药后 15 min 进行． 每次采血 3 ml． 做如下血液流变学检查：1) 全血粘度(η_b)：采用锥板式粘度计(NXE-1)．2)血浆粘度(η_p)： 毛细血管法测定．3) 血细胞比容(Hct)：采用血细胞比积法．4) 纤维蛋白原(Fib)：采用微量热沉淀法．

给药方法

1 *冠脉内给药*　从已插管的远端小动脉(冠脉狭窄上方或下方)接微量恒流输液泵(WSQ-B)连续灌注给药 15 min． 恒流泵输液速度为 0.2 ml／min．

2 *股静脉给药*　使用微量恒流泵灌注 Nic 的方法、时间同冠脉内给药．

冠脉血管阻力分为冠脉血管总阻力(R_T)，大冠脉血管阻力(R_L)和小冠脉血管阻力(R_S)，其计算方法和意义详见前文[4,5]．

实验分为二步

1 *冠脉内(狭窄上方)给药*　设生理盐水组(对照组)、小剂量 Nic (1 μg／kg · min)和大剂量 Nic 组 (5 μg／kg · min)(余同)，每组均 6 条犬．

2 *其它部位给药*　在完成第一步实验后，放松缩窄环，待血液动力学各指标恢复并稳定 30 min 后，再缩窄冠脉，进行此步．设冠脉狭窄下方给小剂量 Nic 组、股 iv 小剂量 Nic 组和大剂量 Nic 组，每组均 6 条犬．

实验数据以 $\bar{x}\pm SD$ 表示、以给药前的值做为对照值，以配对 t 检验处理统计结果．

RESULTS

冠脉内灌注 Nic　分别从冠脉狭窄上方恒流灌注盐水和不同剂量 Nic 15 min 所得血液动力学变化结果见 Tab 1．

灌注盐水和 Nic 后，3 个组的 HR 均无明显改变($P>0.05$)．灌注盐水后，血液动力学各指标无明显变化．灌注 1 μg Nic 后，MAP 无明显变化，DCP 从 5 min 起出现降低且持续至 15 min；CBF 在 1 min 时就出现增高趋势，5 min 起持续增加至 15 min，5 μg Nic 组的血液动力学变化与 1 μg 组相似；但 DCP 减低和 CBF 增加的幅度大于 1 μg 组变化的幅度．

Nic 对冠脉血管阻力的作用　见(Fig 2) 灌注生理盐水对冠脉血管各部位阻力无明显影响．灌注 1 μg Nic 后，R_L 无明显变化，而 R_T 和 R_S 在给药后 5 min 降低并持续至 15 min，分别从 0.87 ± 0.15，0.62 ± 0.13 减低为 0.67 ± 0.12，0.43± 0.11($P<0.01$)灌注 5 μg Nic，R_L 亦无明显变化，R_T 给药 1 min 后即出现减低、15 min 降至最低，从 0.85 ± 0.26 减低为 0.57 ± 0.15；R_S 5 min 出现减低， 15 min 降至最低

Tab 1. Hemodynamic changes during intracoronary infusion of saline and nicorandil (Nic) in case of coronary stenosis $\bar{x}$ **±SD.** $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$, *vs* **control.**

Drug (μg/kg·min)		Normal	Control	Intracoronary infusion time (min) 1	5	10	15
Saline	MAP (kPa)	10.5±1.0	10.3±1.1	10.3±1.1*	10.3±1.1*	10.3±1.1*	10.3±1.1*
	DCP (kPa)	9.8±1.2	7.3±1.4	7.3±1.4*	7.3±1.4*	7.3±1.4*	7.3±1.4*
	CBF (ml/min)	21.5±3.9	14.5±2.4	14.5±1.8*	14.3±1.9*	14.3±1.9*	14.3±2.0*
Nic 1	MAP (kPa)	11.0±1.0	11.2±1.6	11.2±1.6*	11.1±1.7*	11.1±1.7*	11.2±1.6*
	DCP (kPa)	10.2±0.9	7.9±1.5	7.7±1.6*	7.5±1.6**	7.2±1.8***	7.2±1.8**
	CBF (ml/min)	22.4±4.0	13.0±1.7	13.8±2.2*	15.5±1.5***	16.8±1.6***	16.7±2.1***
5	MAP (kPa)	10.1±1.1	10.0±1.3*	10.0±1.3*	10.0±1.3*	9.8±1.4*	9.6±1.5*
	DCP (kPa)	9.8±1.0	7.0±1.6	6.8±1.9*	6.3±2.2*	5.6±1.8**	5.1±1.5**
	CBF (ml/min)	22.2±4.0	12.2±2.3	13.3±2.7*	15.8±2.0**	17.2±1.3***	16.8±1.7**

MAP = mean aortic pressure; DCP = distal coronary pressure; CBF = coronary blood floow

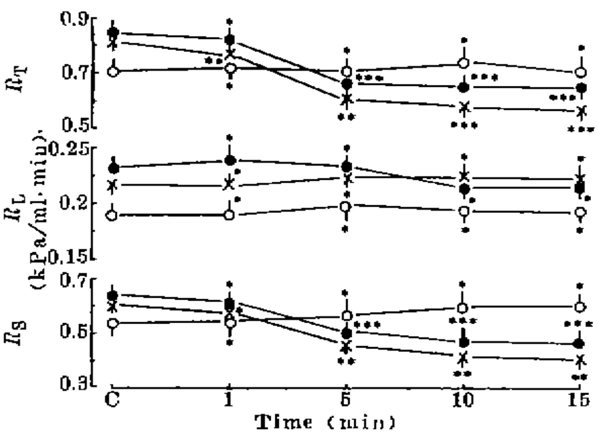

Fig 2. Effects of intracoronary infusion of saline (O) and Nic 1 (●), 5 μg/(kg·min) (×) on coronary vascular resistances in case of coronary artery stenosis. $\bar{x}$ **±SD.** $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* **control (c).**

(从 0.62 ±0.27 减低到 0.31 ±0.10).

Nic 对冠状静脉血液流变学的作用(Tab 2) 灌注生理盐水后，血液流变学各指标无明显变化. 1 μg 的 Nic 使 η_b(5.75s^{-1})降低，余指标无明显变化. 5 μg 的 Nic 使 η_b(230s^{-1})，η_p 和 Hct 均降低；而 Fib 和 η_b(230s^{-1})无明显改变.

其它部位灌注 Nic 由冠脉狭窄下方恒流灌注 1 μg Nic 15 min, HR, MAP 和 R_L 均无明显改变. CBF 从 11.5 ±2.5 增加到 13.2 ±2.9(ml/min, $P<0.01$). DCP 从 7.0 ±1.7 降低到 6.2 ±1.6(kPa, $P<0.01$). R_T 从 1.3 ±0.3 减低到 1.1 ±0.3, R_S 从 0.75 ±0.17 减低到 0.58 ±0.15(kPa/ml·min)冠状静脉中的全血粘度 η_b(5.75 s^{-1})从 25 ±4 降低为 23 ±3 (mP·a)，其它血液流变学指标无明显变化.

为了解 Nic 对体循环的影响，在冠脉狭窄时，分别由股静脉等速等量灌注两种剂量 Nic 15 min 所得结果见 Tab 3.

在两种剂量 Nic 作用下，MAP, R_L 及 HR 均无明显改变，DCP,R_T,R_S 在 5 min 后减低，CBF 在给药后 1 min 无增加趋势，5 min 后增加，这与冠脉内灌注的结果相同.

DISCUSSION

实验表明：两种剂量的 Nic 均能持续增加冠脉狭窄时的血流量，此时伴有远端小动脉压、冠脉血管总阻力和小冠脉血管阻力的减低，这种阻力的减低反映了血管的扩张. 冠脉血管的扩张分为压力性被动扩张和自身主动性扩张. 本文从冠脉或股静脉灌注 Nic 后，血压和心率无明显改变，可以排除压力性因素，反映了药物使冠脉血管主动发生了扩张[7]. 实验也观察到，冠脉内给药 1 min 后，血流量就有增高趋势，并伴有血管阻力的减低；而股静脉给药 1 min 后，血流量和冠脉血管阻力无明显

Tab 2. Changes of blood rheology in coronary vein during intracoronary infusion of saline and Nic in case of coronary stenosis. $n=6$, $\bar{x} \pm SD$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* before.

Drug (μg / kg · min)		η_b(mPa · S) 5.75 s^{-1}	η_b(mPa · S) 230 s^{-1}	η_p(mPa · s)	Fib (mg%)	Hct (%)
Saline	Before	25.0±3.5	7.2±0.9	1.78±0.21	278±117	47.8±4.5
	After	24.9±2.3*	7.0±0.9*	1.83±0.24*	290±100*	47.1±5.1*
Nic 1	Before	25.6±2.8	7.2±0.8	1.83±0.24	280±115	48.8±3.4
	After	21.4±2.3***	6.8±1.1*	1.82±0.20*	284±118*	47.0±4.8*
5	Before	27.1±5.0	7.1±0.9	1.83±0.24	307±104	47.9±2.9
	After	22.5±5.3***	6.6±1 3*	1.75±0 21***	298±130*	45.9±3.9**

η_b = whole blood viscosity; η_p = plasma viscosity; Fib = fibrinogen; Hct: hematocrit

Tab 3. Hemodynamic changes during iv Nic in case of coronary stenosis. $n=6$, $\bar{x} \pm SD$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* control.

Time (min)	MAP (kPa)	DCP (ml / min)	CBF (ml/min)	R_T (kPa/ml · min)	R_L (kPa/ml · min)	R_S (kPa/ml · min)
Nic 1 μg / (kg · min)						
Control	9.6±1.2	6.2±1.1	8.7±1.2	1.13±0.21	0.42±0.12	0.71±0.14
1	9.6±1.2*	6.2±1.1*	8.7±1.2*	1.10±0.24*	0.41±0.13*	0.69±0.15*
5	9.6±1.2*	6.1±1.2*	10.3±2.0***	0.96±0.22***	0.36±0.11*	0.60±0.14***
10	9.5±1.2*	5.7±1.1**	10.5±1.6***	0.95±0.23***	0.38±0.10*	0.55±0.13***
15	9.5±1.2*	5.7±1.2**	10.0±1.5**	0.99±0.26**	0.40±0.11*	0.58±0.17***
Nic 5 μg / (kg · min)						
Control	9.4±1.0	6.2±0.9.	9.8±2.9	1.05±0.39	0.35±0.16	0.69±0.27
1	9.4±0.9*	6.0±0.8*	9.9±3.4*	0.99±0.38*	0.36±0.14*	0.67±0.25*
5	9.5±0.9*	5.8±0.8***	11.7±3.8**	0.91±0.37*	0.34±0.14*	0.56±0.25***
10	9.3±0.9*	5.6±0.8***	11.8±3.3***	0.85±0.32***	0.32±0.14*	0.52±0.20***
15	8.6±1.2*	5.3±0.9**	11.0±3.0**	0.85±0.30**	0.34±0.16*	0.51±0.15**

R_T = total coronary arterial resistance; R_L = large coronary arterial resistance;
R_S = small coronary arterial resistance

改变趋势. 上述结果提示, Nic 对冠脉有直接扩张作用, 它可以选择性地作用于缺血区冠脉, 而对体循环血管似无直接扩张作用. 无论采用冠脉或静脉给药的方法, 其结果一致, 这不同于以往[1,3]的报道.

Gross 等报道[3], Nic 对正常冠脉无明显作用; 但对缺血时冠脉能增加心外膜向心内膜的血流量. 然而他们没有测冠脉各部分血管阻力的变化. Preuss[1]在清醒犬上观察到, 大剂量 Nic 可降低血压, 增加心率和心缩力, 这一作用不是通过 β 受体兴奋起作用的. 但是, 他们不能解释 Nic 是对冠脉直接作用还是通过体循环的间接作用.

实验也观察到, Nic 在扩张冠脉的同时, 能降低缺血区血液粘度, 小剂量能降低低切血粘, 大剂量能降低低切血粘、血浆粘度和血细胞比容. 这有利于改善缺血区心肌的高血粘状态和微循环障碍[8].

Nic 扩血管的机理至今仍不很清楚. 有人认为与血管平滑肌受体变化有关[3]; 有人认为与抑制钙离子有关[9]. 它对于缺血区血液流变学的作用也未见报道. 故需进一步研究.

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苦参碱的抗心律失常作用

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Anti-arrhythmic effects of matrine

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ABSTRACT Matrine (MT) is an alkaloid isolated from *Sophra alopecuroids* L. The LD_{50} of MT iv to mice was 72.1 mg / kg (95% CL 68.2–76.5 mg / kg). MT had significant effects on different experimental models of arrhythmias induced by aconitine, barium chloride or coronary ligation. The ECG of anesthetized rats was significantly changed after iv of MT. The HR was retarded and the PR and QT_c intervals were prolonged.

MT decreased the normal spontaneous beating in isolated rat atria and decreased the automaticity induced by norepinephrine in isolated rat ventricle. MT decreased the speed-up effect of isoproterenol on spontaneous beating rate in rat isolated atria. MT had no effect on the contraction of rabbit aorta strips induced by norepinephrine and rat taenia coli depolarized by high K^+. MT had negative chronotropic, negative automaticity and negative conduction effects. These actions may be the pharmacological basis for its anti-arrhythmic effects.

KEY WORDS matrine; arrhythmia; aconitine; barium chloride; heart atrium; heart ventricle; thoracic aorta

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提要 大鼠 iv 苦参碱 (MT) 能显著对抗乌头碱、氯化钡和结扎冠脉所致的心律失常. iv MT 18.75 mg / kg, 心率明显减慢, P–R 和 Q–T_c 间期明显延长. MT 200 μmol / L 显著减慢离体大鼠右心房自发频率, 拮抗 Iso 诱发的心率加快, 量–效曲线非平行右移, 并明显拮抗离体大鼠左心室由 NE 诱发的心率加