临床研究论著

# 冠脉慢性完全闭塞病变介入治疗术后早期支架内再狭窄的影响因素分析

田留洋[1]，刘昱圻[2]，杨美艳[2]，强钰伟[2]，李 泱[2]
[1]南开大学医学院，天津 300071；[2]解放军总医院 心血管内科，北京 100853

**摘要：目的** 探讨冠状动脉慢性完全闭塞病变 (chronic total occlusion，CTO) 经皮介入治疗 (percutaneous coronary intervention，PCI) 术后早期发生支架内再狭窄 (in-stent restenosis，ISR) 的影响因素。**方法** 分析 2003 年 11 月 – 2015 年 7 月于解放军总医院接受冠状动脉造影 (coronary angiography，CAG) 并成功置入药物涂层支架后发生支架内再狭窄的 54 例患者的临床资料。根据心肌缺血症状和造影证据显示的发生支架内再狭窄的时间分为早期支架内再狭窄和晚期支架内再狭窄。采用单因素及 Logistic 多因素分析 CTO 病变 PCI 术后发生 ISR 的影响因素。**结果** 54 例 CTO 患者共 76 个支架内再狭窄，其中早期支架内再狭窄 7 个 (9.2%)，晚期支架内再狭窄 69 个 (90.8%)。早期支架内再狭窄组纤维蛋白原水平 (*P*=0.001)、尿酸水平 (*P*=0.023) 高于晚期支架内再狭窄组；早期支架内再狭窄组血清总胆红素水平 (*P*=0.041)、血清直接胆红素水平 (*P*=0.035) 低于晚期支架内再狭窄组。Logistic 多元回归分析显示，血清纤维蛋白原 (*OR*=0.314，95% *CI*：0.138 ~ 0.714，*P*=0.006)，尿酸 (*OR*=0.988，95% *CI*：0.978 ~ 0.999，*P*=0.028) 和血清总胆红素 (*OR*=1.453，95% *CI*：1.113 ~ 1.896，*P*=0.006) 是早期冠脉支架内再狭窄的独立危险因素。**结论** 高血清纤维蛋白原、高尿酸、低总胆红素促进早期冠脉支架内再狭窄形成。

**关键词：**冠状动脉；慢性完全闭塞病变；支架内再狭窄；经皮介入治疗
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## Influential factors of early in-stent restenosis in patients with coronary chronic total occlusion after percutaneous coronary intervention

TIAN Liuyang[1], LIU Yuqi[2], YANG Meiyan[2], QIANG Yuwei[2], LI Yang[2]
[1]Department of Medical School, Nankai University, Tianjin 300071, China; [2]Department of Cardiology, Chinese PLA General Hospital, Beijing 100853, China
Corresponding author: LI Yang. Email: liyangbsh@163.com

**Abstract: Objective** To investigate the influential factors of early in-stent restenosis (ISR) in patients with coronary chronic total occlusion (CTO) after percutaneous coronary intervention (PCI). **Methods** Clinical data about 54 patients who had undergone coronary angiography (CAG) and implanted drug-eluting stents (DES) with ISR in Chinese PLA General Hospital from November 2003 to July 2015 were analyzed retrospectively. All patients were divided into two groups by time of ISR. The risk factors of ISR were analyzed by univariate analysis and multiple Logistic regression analysis. **Results** There were 76 ISR in 54 patients with CTO, with early ISR rate of 9.2% (7) and late ISR rate of 90.8% (69). Compared with late ISR group, the level of fibrinogen and uric acid (UA) in early ISR group was significantly higher (*P*=0.001, *P*=0.023), while the level of serum total bilirubin and serum direct bilirubin was significantly lower (*P*=0.041, *P*=0.035). Multiple Logistic regression analysis showed fibrinogen [*OR*=0.314, 95% *CI* (0.138-0.714)](*P*=0.006), uric acid (UA) [*OR*=0.988, 95% *CI* (0.978-0.999)] (*P*=0.028) and total bilirubin [*OR*=1.453, 95% *CI* (1.113-1.896)] (*P*=0.006) were independent predictors for early ISR after PCI. **Conclusion** Elevated fibrinogen level, elevated uric acid level, and low total bilirubin level are risk factors of early ISR after PCI.
**Keywords:** coronary artery; chronic total occlusion; in-stent restenosis; percutaneous coronary intervention

根据 2007 年美国心脏学会 (American Heart Association，AHA)/ 美国心脏病学会 (American College of Cardiology，ACC) 定义，慢性完全闭塞病变 (chronic totaloc clusion，CTO) 为闭塞时间≥ 3 个月的病变[1]，根据是否存在前向血流，又可将慢性完全闭塞病变分为慢性功能性闭塞 ( 前向血流 TIMI1 级 ) 和慢性完全性闭塞 ( 前向血流 TIMI0 级 )[2]。冠状动脉慢性完全闭塞病变因其特殊的病理特点，较非 CTO 病变血管再通成功率低、操作复杂、并发症发生率高、远期预后不良[3]。药物洗脱支架 (drug eluting stent，DES) 的应用大幅降低了经皮介入治疗术 (percutaneous coronary intervention，PCI)

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Supported by the National Natural Science Foundation of China(81030002)
**作者简介：**田留洋，女，在读硕士。研究方向：心血管内科。Email: tianly0909@163.com
**通信作者：**李泱，男，博士，研究员，教授，博士生导师。Email: liyangbsh@163.com

后的再狭窄率，已成为 PCI 打通 CTO 的常规选择，但术后仍然可能发生再狭窄 [4]。冠状动脉支架内再狭窄是指在冠状动脉病变处置入支架后，支架内发生再次狭窄，并经冠状动脉造影证实。本研究分析 CTO 回访病例的临床资料、冠脉造影影像资料等，探讨置入 DES 治疗 CTO 后早期和晚期发生支架内再狭窄 (in-stent restenosis，ISR) 的影响因素。

## 资料和方法

**1** 一般资料　选择 2003 年 11 月 - 2015 年 7 月于解放军总医院接受冠状动脉造影 (coronary angiography，CAG) 并成功置入药物支架后发生支架内再狭窄的 54 例 CTO 患者的临床资料。

**2** 研究方法　CAG 随访后，根据心肌缺血症状和造影结果证据显示的发生支架内再狭窄的时间分为两组：1) 早期支架内再狭窄：支架置入 30 d 内进行冠状动脉造影见支架置入部位发生再狭窄；2) 晚期支架内再狭窄：支架置入 > 30 d 时支架置入部位发生再狭窄 [5]。比较两组临床资料、冠脉造影影像资料等方面的差异。

**3** 统计学处理　采用 SPSS17.0 统计软件进行数据录入和分析。计量资料以 $\bar{x} \pm s$ 表示，计数资料以百分数 (%) 表示。计量资料比较采用独立样本 $t$ 检验，计数资料比较采用 $\chi^2$ 检验或 Fisher 精确检验。采用 Logistic 回归分析患者术后发生早期 ISR 的影响因素。$P < 0.05$ 为差异有统计学意义。

## 结　果

**1** 两组基线资料比较　54 例 CTO 患者共 76 个支架内再狭窄，其中早期支架内再狭窄 7 例 (9.2%)，晚期支架内再狭窄 69 例 (90.8%)( 图 1)。早期支架内再狭窄组与晚期支架内再狭窄组年龄、性别、吸烟史、高血压史高脂血症史、糖尿病史、心肌梗死史、脑血管病史、支架总长度差异均无统计学意义 ( 表 1)。

**2** 两组生化指标比较　早期支架内再狭窄组纤维蛋白原水平、尿酸水平高于晚期支架内再狭窄组 ($P < 0.05$)；早期支架内再狭窄组血清总胆红素水平、血清直接胆红素水平低于晚期支架内再狭窄组 ($P < 0.05$)( 表 2)。

**表 1　早期支架内再狭窄组与晚期支架内再狭窄组临床基线资料比较**

**Tab. 1　Baseline data of early stent restenosis patients and late stent restenosis patients**

| Item | Early stent restenosis patients (n=7) | Late stent restenosis patients (n=69) | *P* |
|---|---|---|---|
| Sex | | | 0.510 |
| Male (n, %) | 6(87.5) | 64(92.8) | |
| Female (n, %) | 1(12.5) | 5(7.2) | |
| Age (yrs) | 64.7 ± 12.5 | 59.4 ± 14.3 | 0.768 |
| Smoking history (n, %) | 3(42.9) | 48(69.9) | 0.154 |
| Hypertension (n, %) | 2(28.6) | 28(40.8) | 0.536 |
| Hyperlipidemia (n, %) | 1(14.3) | 25(36.0) | 0.254 |
| Diabetes (n, %) | 4(51.7) | 25(36.0) | 0.282 |
| Myocardial infarction (n, %) | 1(14.3) | 10(14.0) | 0.984 |
| Cerebrovascular disease (n, %) | 1(14.3) | 4(69.0) | 0.422 |
| Stent length (mm) | 62.7 ± 36.3 | 54.2 ± 33.4 | 0.862 |

**表 2　早期支架内再狭窄组与晚期支架内再狭窄组生化指标比较**

**Tab. 2　Comparison of biochemical markers between early stent restenosis patients and late stent restenosis patients** ($\bar{x} \pm s$)

| Item | Early stent restenosis patients (n=7) | Late stent restenosis patients (n=69) | *P* |
|---|---|---|---|
| Cholesterol (mmol/L) | 4.1 ± 0.8 | 5.1 ± 1.2 | 0.310 |
| TG (mmol/L) | 1.1 ± 0.6 | 1.52 ± 0.75 | 0.385 |
| LDL (mmol/L) | 2.67 ± 0.7 | 2.16 ± 0.73 | 0.078 |
| Fibrinogen (g/L) | 4.55 ± 1.21 | 3.34 ± 0.88 | 0.001 |
| Cr (μmol/L) | 82.6 ± 20.1 | 83.3 ± 26.1 | 0.946 |
| ALT (U/L) | 22.4 ± 14.8 | 26.5 ± 24.3 | 0.731 |
| AST (U/L) | 36.2 ± 42.4 | 25.7 ± 22.3 | 0.297 |
| Uric acid (μmol/L) | 399.6 ± 68.8 | 326.4 ± 80.5 | 0.023 |
| Total bilirubin (μmol/L) | 10.6 ± 3.0 | 17.0 ± 8.1 | 0.041 |
| Direct bilirubin (μmol/L) | 2.2 ± 0.9 | 3.8 ± 1.9 | 0.035 |

**3** Logistic 多元回归分析　选择单因素分析中有统计学差异的纤维蛋白原、总胆红素、直接胆红素、尿酸为自变量，以术后早期支架内再狭窄为因变量行 Logistic 多元回归分析，结果显示血清纤维蛋白原 (*OR*=0.314，95% *CI*：0.138 ~ 0.714)，尿酸 (*OR*=0.988，95% *CI*：0.978 ~ 0.999) 和血清总胆红素 (*OR*=1.453，95% *CI*：1.113 ~ 1.896) 是早期冠脉支架内再狭窄的独立危险因素 ( 表 3)。

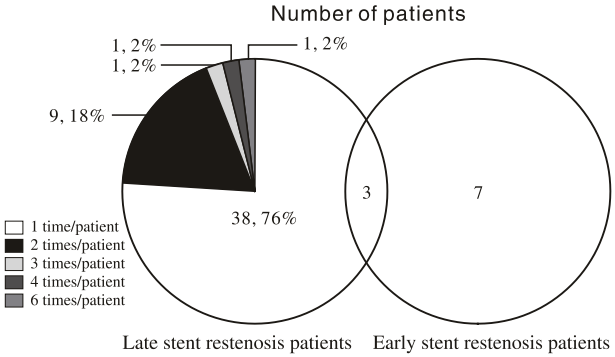


**图 1　两组患者支架内再狭窄发生次数比较**

**Fig.1　Comparison of times of ISR in two groups**

**表 3　Logistic 多元回归分析结果**

**Tab. 3　Multiple Logistic regression analysis results**

| Item | *B* | $\chi^2$ | *P* | *OR* (95% *CI*) |
|---|---|---|---|---|
| Fibrinogen | 1.160 | 7.621 | 0.006 | 0.314(0.138–0.714) |
| Total bilirubin | –0.373 | 7.539 | 0.006 | 1.453(1.113–1.896) |
| Direct bilirubin | –0.626 | 2.713 | 0.100 | 1.870(0.888–3.939) |
| Uric acid | 0.012 | 4.815 | 0.028 | 0.988(0.978–0.999) |

## 讨　论

PCI 术后发生 ISR 的问题长期以来一直备受关注。应用金属裸支架 (bare-metal stent，BMS) 开展的多个大规模临床随机研究表明，与单纯经皮冠状动脉腔内血管成形术 (percutaneous transluminal coronary angioplasty，PTCA) 相比，支架置入术可显著降低 CTO 的再狭窄率，但 BMS 再狭窄率仍然很高，影响远期效果，DES 大幅降低了 PCI 术后 ISR[6]。

本研究结果发现，早期支架内再狭窄组纤维蛋白原水平明显高于晚期支架内再狭窄组。多因素 Logistic 回归分析发现，*OR*=0.314，95% *CI*：0.138 ~ 0.714。Lupi 等 [7] 研究发现，支架内再狭窄患者的血浆纤维蛋白原水平明显高于支架内未再狭窄患者。血浆纤维蛋白原水平对心血管疾病的预后有 34% ~ 50% 的预测价值 [8]，纤维蛋白原本质为一种急性血浆糖蛋白，能够参加体内的免疫活性和炎性反应，促进血小板的聚集，参与血液凝固和动脉粥样硬化 [9–11]。

本研究中早期支架内再狭窄组尿酸水平高于晚期支架内再狭窄组。多因素 Logistic 回归分析显示，提示尿酸 (*OR*=0.988，95% *CI*：0.978 ~ 0.999) 是早期冠脉支架内再狭窄的独立危险因素。Neogi 等 [12] 研究中提示尿酸是冠状动脉粥样硬化以及冠脉钙化的危险因素 [13–14]。尿酸是机体内嘌呤核酸分解代谢的终末产物，升高的尿酸促进低密度脂蛋白胆固醇的氧化和脂质过氧化，尿酸盐结晶可以沉积于动脉壁，导致动脉内膜损伤而引起动脉硬化 [15]。

本研究发现，早期支架内再狭窄组血清总胆红素水平低于晚期支架内再狭窄组；多因素 Logistic 回归分析显示，血清总胆红素 (*OR*=1.453，95% *CI*：1.113 ~ 1.896) 是早期冠脉支架内再狭窄的独立危险因素。近年的研究表明，胆红素是内源性、生理性抗氧化剂，可抑制脂质尤其是低密度脂蛋白的氧化修饰并清除氧自由基 [16]，减少动脉粥样硬化发生 [17–18]。

综上可知，血清纤维蛋白原、尿酸、胆红素水平与早期冠脉支架内再狭窄的发生具有相关性。但本研究为回顾性研究，不能完全排除病例选择偏倚因素。另外本研究样本量较小，需增加样本量进一步探讨。

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