

· 临床研究 ·

小而密低密度脂蛋白胆固醇与冠心病患者经皮冠状动脉介入治疗术后围术期心肌损伤的相关性

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【摘要】 目的 探讨小而密低密度脂蛋白胆固醇(sdLDL-C)与冠心病患者经皮冠状动脉介入治疗(PCI)围术期心肌损伤(PMI)的相关性及其预测价值。**方法** 选取2021年1月至2022年6月在江苏大学附属宜兴医院行择期PCI治疗的冠心病患者141例,包括心绞痛98例和急性心肌梗死43例;以及同期非冠心病66例。收集临床基线资料及术中冠状动脉病变情况,常规检测术前血脂以及术前术后心肌肌钙蛋白I(cTnI)等指标。接受PCI治疗的患者根据术后cTnI是否升高分为观察组(cTnI升高, $n=86$)和对照组(cTnI正常, $n=55$),对比2组间各项指标的差异。同时比较非冠心病,心绞痛,急性心肌梗死3组间sdLDL-C水平的差异。采用SPSS 16.0软件进行数据分析。根据数据类型,组间比较分别采用 t 检验及 χ^2 检验。3组之间两两比较采用方差分析及趋势检验。采用二分类logistic回归分析评价sdLDL-C与术后cTnI升高的关系。**结果** 观察组sdLDL-C、总胆固醇、低密度脂蛋白胆固醇(LDL-C)、植入支架数、支架总长度均高于对照组,差异均有统计学意义[(0.74 ± 0.26) 和(0.56 ± 0.27) mmol/L, (4.51 ± 1.17) 和(3.90 ± 1.04) mmol/L, (2.77 ± 0.80) 和(2.25 ± 0.73) mmol/L, (1.74 ± 0.91) 和(1.33 ± 0.62), (52.52 ± 27.93) 和(36.92 ± 19.41) mm;均 $P<0.05$]。logistic回归分析显示,sdLDL-C($OR=14.798,95\%CI 1.112\sim196.904$),LDL-C($OR=3.074,95\%CI 1.138\sim8.302$)是冠心病患者PCI术后PMI的独立危险因素($P<0.05$)。sdLDL-C在受试者工作特征(ROC)曲线下面积是0.727($95\%CI 0.637\sim0.817, P<0.05$),最佳截断值为0.518 mmol/L,诊断PMI灵敏度为86.0%,特异度为56.4%,约登指数为0.424。非冠心病、心绞痛、急性心肌梗死3组的sdLDL-C分别是(0.541 ± 0.144), (0.621 ± 0.257), (0.776 ± 0.289) mmol/L,两两比较差异均有统计学意义($P<0.05$),呈显著上升趋势($P<0.05$)。**结论** 术前高水平sdLDL-C是冠心病患者PCI术后围术期心肌损伤的危险因素,sdLDL-C与疾病严重程度呈正相关。

【关键词】 小而密低密度脂蛋白胆固醇;经皮冠状动脉介入治疗;围术期心肌损伤

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Correlation between small dense low-density lipoprotein cholesterol and peri-operative myocardial injury in patients with coronary heart disease after PCI

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【Abstract】 Objective To investigate the correlation between small dense low-density lipoprotein cholesterol (sdLDL-C) and peri-operative myocardial injury (PMI) in patients with coronary heart disease (CHD) after percutaneous coronary intervention (PCI) and the predictive value of sdLDL-C for PMI. **Methods** A total of 141 CHD patients, 98 with angina and 43 with acute myocardial infarction, were retrospectively selected as the research subjects, who received elective PCI from January 2021 to June 2022, and 66 non-CHD individuals were selected during the same time. The clinical baseline data were collected, the distribution pattern of coronary lesions were recorded intraoperatively, and indexes such as the preoperative blood lipids and postoperative cardiac tropomom I (cTnI) were routinely tested. According to the postoperative cTnI value, the PCI patients were divided into the observation group with elevated cTnI level ($n=86$) and the control group with normal cTnI level ($n=55$). The two groups were compared for all the collected parameters, and the non-CHD group, the angina group and the acute myocardial infarction group were compared for sdLDL-C levels. SPSS 16.0 was used for statistical analysis. Data comparison between groups was performed using t -test or χ^2 test, depending on data type. Analysis of variance and trend testing were used for pairwise comparison among the three groups. The relationship between sdLDL-C and postoperative cTnI elevation was evaluated using binary logistic regression analysis. **Results** sdLDL-C, total cholesterol, low-density lipoprotein cholesterol (LDL-C), numbers of implanted stents, and total length of the stents in the observation group were significantly higher than those in the

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control group[(0.74±0.26) vs (0.56±0.27) mmol/L, (4.51±1.17) vs (3.90±1.04) mmol/L, (2.77±0.80) vs (2.25±0.73) mmol/L, (1.74±0.91) vs (1.33±0.62), (52.52±27.93) vs (36.92±19.41) mm, all $P<0.05$]. The logistic regression analysis showed that sdLDL-C ($OR=14.798$, 95% CI 1.112–196.904) and LDL-C ($OR=3.074$, 95% CI 1.138–8.302) were the independent risk factors of PMI ($P<0.05$). The area under ROC curve for sdLDL-C was 0.727 (95% CI 0.637–0.817; $P<0.05$) with the best cut-off point of 0.518 mmol/L, and a sensitivity of 86.0% and a specificity of 56.4% for the diagnosis of PMI, and the Youden index was 0.424. sdLDL-C was (0.541±0.144) mmol/L in the non-CHD group, (0.621±0.257) mmol/L in the angina group, and (0.776±0.289) mmol/L in the acute myocardial infarction group, with significant differences between groups ($P<0.05$) and a significant upward trend ($P<0.05$). **Conclusion** The preoperative high level of sdLDL-C is a risk factor of PMI after PCI in the CHD patients, and sdLDL-C has a positive correlation with the severity of the disease.

【Key words】 small dense low-density lipoprotein cholesterol; percutaneous coronary intervention; perioperative myocardial injury

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近年来,我国冠心病的发病率和死亡率呈显著上升趋势,在居民死亡构成比中扮演了重要角色^[1]。经皮冠状动脉介入治疗(percutaneous coronary intervention, PCI)已经成为冠心病的主要治疗手段之一,2018年我国 PCI 总量逾 91.5 万例,居全球首位^[2]。而 PCI 相关围术期心肌损伤(periooperative myocardial injury, PMI)因其显著影响患者预后而备受关注。PMI 是指术前肌钙蛋白正常,术后超过正常值上限 99 个百分位数;或术前值超上限但趋于稳定或下降趋势,术后值较术前值增加>20%^[3]。既往研究发现,患者疾病状态、冠状动脉病变情况、术中操作等因素影响 PMI 发生^[4,5]。本研究对 PMI 危险因素的研究发现脂蛋白相关磷脂酶 A2、脂蛋白(a)与 PMI 具有相关性,可作为术前预测因子^[6,7]。小而密低密度脂蛋白胆固醇(small dense low-density lipoprotein cholesterol, sdLDL-C)作为低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)的重要亚组,其致动脉粥样硬化(atherosis, AS)作用更明显,与冠状动脉痉挛、血管病变严重程度具有显著相关性^[8],但其与 PMI 之间的关系鲜有报道。本研究旨在通过分析 sdLDL-C 与 PMI 之间的关系,阐明 sdLDL-C 对冠心病患者 PCI 术后发生 PMI 的预测价值。

1 对象与方法

1.1 研究对象

纳入 2021 年 1 月至 2022 年 6 月在江苏大学附属宜兴医院确诊为冠心病且行择期 PCI 治疗患者 141 例作为冠心病组,包括心绞痛 98 例、急性心肌梗死 43 例,以及同期经冠状动脉造影(coronary angiography, CAG)或者冠状动脉 CTA 检查明确排除冠心病共 66 例作为非冠心病组,收集所有对象临床基线资料。冠心病组纳入标准:(1)术前心肌肌钙蛋白 I(cardiac troponin I, cTnI)阴性;(2)单次 PCI 治疗并完成血运重建。排除标准:(1)术前 cTnI 阳性;(2)CAG 显示严重钙化或血栓性病变;(3)急性感染性疾病;(4)严重器质性疾病,如严重肝肾功能

不全、严重心力衰竭(心功能纽约分级Ⅲ~Ⅳ级);(5)急性脑卒中。本研究经医院伦理委员会通过伦理审批(伦审 2023 科 018)。

1.2 方法

所有纳入冠心病组的急性心肌梗死患者因错过急诊介入时间窗而行择期血运重建,且术前 cTnI 阴性。所有 PCI 患者术后 8、16、24 h 共检测 cTnI 3 次,其中至少 1 次超过正常上限 99 个百分位数视为心肌损伤,为观察组 86 例;术后 3 次 cTnI 均未升高为对照组 55 例。

1.2.1 临床基线资料 收集所有对象一般临床基线资料,包括性别、年龄、高血压史、糖尿病史、吸烟史、饮酒史、既往 PCI 手术史、甘油三酯(triglyceride, TG)、总胆固醇(total cholesterol, TC)、高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)、LDL-C、sdLDL-C、游离脂肪酸(free fatty acid, FFA),以及手术时长、冠状动脉病变情况、植入支架数、植入支架总长度等指标。

1.2.2 CAG 及 PCI 术 在 PMI 的影响因素中,术者的操作是最主要因素之一,故本研究介入操作均由同一位经验丰富的介入医师完成。根据 CAG 结果,冠状动脉狭窄 $\geq 50\%$ 且病变累及主要冠状动脉诊断为冠心病,靶病变是否需要血运重建遵循介入治疗指南^[9]。术中尽可能采取“简单策略”处理病变血管,如减少球囊扩张次数等以期减少不必要的心肌损伤。

1.2.3 血样采集及检测 所有对象术前清晨抽取肘静脉血行生化检测。术前及术后采集静脉血 3 ml 检测 cTnI,采用 NRM411-S7 型全自动化学发光测定仪(南京 NORMAN 公司)及其配套试剂,严格遵循设备操作流程。

1.3 统计学处理

采用 SPSS 16.0 统计软件进行数据分析。计量资料用均数±标准差($\bar{x}\pm s$)表示,采用 t 检验;3 组之间两两比较采用方差分析及趋势检验。计数资料用例数(百分率)表示,采用 χ^2 检验。采用二分类 logistic 回归分析评价 sdLDL-C 与术后 cTnI 升高的

关系。 $P<0.05$ 为差异有统计学意义。

2 结 果

2.1 临床基线资料特点

PCI 患者根据术后 cTnI 是否升高分为观察组 ($n=86$) 和对照组 ($n=55$), 2 组患者年龄、性别、高血压史、糖尿病史、吸烟史、饮酒史、既往 PCI 手术史、TG、HDL-C、FFA、手术时长、多支病变、分叉病变及长病变情况比较, 差异均无统计学意义; sdLDL-C、LDL-C、TC、植入支架数及支架总长度情况比较, 差异均有统计学意义(均 $P<0.05$; 表 1)。

2.2 冠心病患者 PMI 危险因素分析

二分类 logistic 回归分析结果显示, sdLDL-C、LDL-C 是冠心病患者 PCI 术后发生 PMI 的独立危险因素 ($P<0.05$); 而 TC、植入支架数、支架总长度差异均无统计学意义(表 2)。

2.3 sdLDL-C、LDL-C 预测围术期心肌损伤受试者工作特征曲线分析

受试者工作特征(receiver operating characteristic,

ROC) 曲线分析结果显示, ROC 曲线下面积在 sdLDL-C 为 0.727(95%CI 0.637~0.817; $P<0.05$), LDL-C 为 0.699(95%CI 0.608~0.790; $P<0.05$), 详见图 1。根据 Youden 指数计算 sdLDL-C 在 ROC 上最佳截断值为 0.518 mmol/L, 诊断 PMI 灵敏度、特异度分别为 86.0%、56.4%, 约登指数 0.424; LDL 最佳截断值 2.37 mmol/L, 诊断 PMI 灵敏度 69.8%, 特异度 67.3%, 约登指数 0.371。

2.4 sdLDL-C 与疾病分组的关系

比较非冠心病、心绞痛、急性心肌梗死 3 组结果显示, sdLDL-C 在 3 组中分别为 (0.541 ± 0.144), (0.621 ± 0.257), (0.776 ± 0.289) mmol/L, 3 组之间两两比较差异均有统计学意义(均 $P<0.05$), 趋势检验结果显示, sdLDL-C 水平在上述 3 组中呈显著上升趋势 ($P<0.05$; 图 2)。而 LDL-C 在急性心肌梗死组[(2.93 ± 0.78) mmol/L] 显著高于非冠心病组[(2.44 ± 0.60) mmol/L] 和心绞痛组[(2.41 ± 0.78) mmol/L], 差异均有统计学意义(均 $P<0.05$), 但非冠心病组和心绞痛组之间差异无统计学意义。

表 1 2 组患者基线资料比较

Table 1 Comparison of baseline data between two groups

Item	Observation group ($n=86$)	Control group ($n=55$)	P value
Age (years, $\bar{x}\pm s$)	64.43 $\pm$ 10.47	64.98 $\pm$ 9.93	0.756
Male[n (%)]	75(87.21)	42(76.36)	0.096
Hypertension[n (%)]	56(65.88)	41(74.55)	0.281
Diabetes mellitus[n (%)]	30(35.29)	25(45.45)	0.232
Smoking[n (%)]	48(56.47)	24(43.64)	0.141
Alcohol drinking[n (%)]	14(16.47)	10(18.18)	0.795
History of PCI[n (%)]	21(24.71)	17(30.91)	0.448
TG (mmol/L, $\bar{x}\pm s$)	1.90 $\pm$ 1.72	1.83 $\pm$ 1.15	0.811
TC (mmol/L, $\bar{x}\pm s$)	4.51 $\pm$ 1.17	3.90 $\pm$ 1.04	0.002
HDL-C (mmol/L, $\bar{x}\pm s$)	1.07 $\pm$ 0.16	1.06 $\pm$ 0.21	0.888
LDL-C (mmol/L, $\bar{x}\pm s$)	2.77 $\pm$ 0.80	2.25 $\pm$ 0.73	<0.001
sdLDL-C (mmol/L, $\bar{x}\pm s$)	0.74 $\pm$ 0.26	0.56 $\pm$ 0.27	<0.001
FFA (mmol/L, $\bar{x}\pm s$)	0.51 $\pm$ 0.29	0.44 $\pm$ 0.23	0.169
Operation time (min, $\bar{x}\pm s$)	86.98 $\pm$ 35.41	87.44 $\pm$ 40.91	0.944
Multivessel lesions[n (%)]	67(79.77)	44(80.00)	0.472
Bifurcation lesions[n (%)]	7(8.33)	4(7.27)	0.822
Long lesions[n (%)]	70(83.33)	41(74.55)	0.209
Numbers of stents ($\bar{x}\pm s$)	1.74 $\pm$ 0.91	1.33 $\pm$ 0.62	0.006
Total length of stents (mm, $\bar{x}\pm s$)	52.52 $\pm$ 27.93	36.92 $\pm$ 19.41	0.001

TG: triglyceride; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; sdLDL-C: small dense low-density lipoprotein cholesterol; FFA: free fatty acid.

表 2 冠心病患者 PMI 的危险因素分析

Table 2 Analysis of risk factors of PMI in CHD patients

Factor	B	SE	$Wald\ \chi^2$	df	OR	95%CI	P value
TC	-0.771	0.446	2.980	1	0.463	0.193-1.110	0.084
LDL-C	1.123	0.507	4.910	1	3.074	1.138-8.302	0.027
sdLDL-C	2.695	1.321	4.163	1	14.798	1.112-196.904	0.041
Numbers of stents	0.369	0.780	0.223	1	1.446	0.313-6.672	0.637
Total length of stents	0.014	0.023	0.374	1	1.014	0.969-1.062	0.541

TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; sdLDL-C: small dense low-density lipoprotein cholesterol; PMI: perioperative myocardial injury; CHD: coronary heart disease.

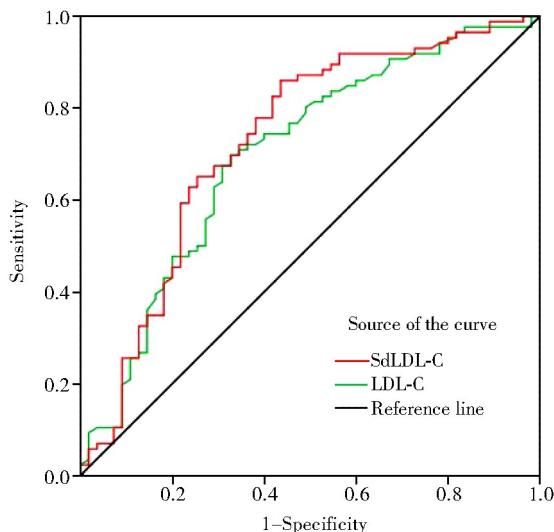


图 1 sdLDL-C 和 LDL-C 预测围术期心肌损伤的 ROC 曲线分析

Figure 1 ROC curve analysis of sdLDL-C and LDL-C in predicting perioperative myocardial injury

ROC: receiver operating characteristic; sdLDL-C: small dense low density lipoprotein cholesterol; PMI: perioperative myocardial injury.

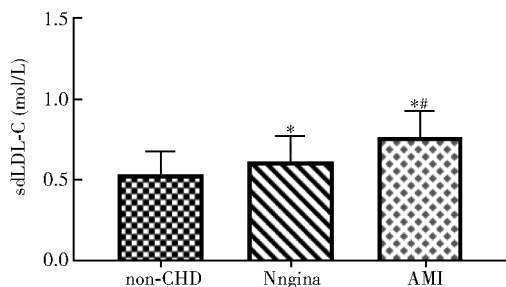


图 2 sdLDL-C 与疾病分组的关系

Figure 2 Relationship between sdLDL-C and diseases

sdLDL-C: small dense low-density lipoprotein cholesterol; non-CHD: non coronary heart disease; AMI: acute myocardial infarction. Compared with non-CHD group, * $P<0.05$; compared with angina group # $P<0.05$.

3 讨论

脂代谢异常是 AS 发展过程中重要的病理机制, LDL-C、TC、TG 升高以及 HDL-C 降低均与 AS 具有显著相关性^[10]。然而临床实践中发现积极控制上述血脂达标后仍有部分患者发生心血管事件且预后不良^[11]。近期研究发现 sdLDL-C 是心血管疾病的独立危险因素, 其风险评估价值甚至优于 TC、LDL-C 等传统危险因素^[12,13]。sdLDL-C 是由极低密度脂蛋白经过水解、转化、脱酯生成更小更致密的脂蛋白, 其直径 $<25.5\text{ nm}$, 密度 $>1.034\text{ g/ml}$ 。LDL-C 具有多分散度以及异质性的特点, 而 sdLDL-C 被认为是 LDL-C 促进动脉粥样硬化的主要亚型已经达成共识^[14,15]。sdLDL-C 的致病机制可能涉及以下几个方面。(1)sdLDL-C 分子内的载脂蛋白 B 在脱酯水解过程中空间构象发生变化, 使肝细胞与 LDL-C

亲和力降低, 减缓分解速率, 增强了对血管壁的“锚定”作用; 又因为 sdLDL-C 密度大, 颗粒小, 数量多, 更容易穿过血管内皮, 从而促进脂质沉积加速动脉硬化。(2)sdLDL-C 中唾液酸含量少, 表面易暴露, 去乙酰化作用显著增加了 sdLDL-C 与血管壁上阴离子蛋白多糖的亲和力, 加速了脂质的跨膜运输、沉积转变为泡沫细胞。(3)sdLDL-C 可介导 LDL-C 发生氧化反应生成氧化型 LDL-C, 同时减少抗氧化物的生成, 引起血管内皮功能障碍, 黏附分子、趋化因子聚集, 介导单核细胞浸润转化为巨噬细胞并大量吞噬脂质, 这一过程加速了动脉硬化进程, 同时增加了动脉斑块内脂质含量, 使得斑块不稳定性增加^[16,17]。由此可见, 相较于 LDL-C, sdLDL-C 具有更强的促动脉粥样硬化作用, 而且围术期高水平 sdLDL-C 容易导致急性内皮功能障碍、泡沫细胞聚集以及不稳定斑块增加, 促使冠状动脉内急性血栓形成或者斑块破裂造成微循环障碍。血栓形成和斑块破裂是 PMI 发生的主要原因, 由此我们推测, sdLDL-C 可作为 PMI 发生的潜在预测因子。

本研究发现, sdLDL-C、LDL-C、TC、植入支架数、支架总长度在对照组中明显高于观察组, logistic 回归分析结果显示 sdLDL-C、LDL-C 是 PMI 的独立危险因素, 可能原因是急性血栓形成、不稳定斑块破裂、微循环障碍致使心肌损伤。sdLDL-C、LDL-C 的 ROC 曲线下面积分别为 0.727、0.699, 相较于 LDL-C, sdLDL-C 有更好的预测 PMI 价值。此外 sdLDL-C 在非冠心病组、心绞痛组、急性心肌梗死组呈显著上升趋势, 提示 sdLDL-C 与冠心病严重程度相关, 这与既往研究结果相一致^[18]。由此本研究得出初步结论, sdLDL-C 可作为冠心病患者 PCI 术后发生 PMI 的潜在预测因子。既往研究表明, 他汀可有效降低 sdLDL-C 水平及心血管不良事件的发生率^[19]; 中医药在降脂治疗中也扮演重要角色, 特别是他汀不耐受或者他汀治疗仍未达标患者具有良好的协同治疗作用, 能有效降低 sdLDL-C 水平^[20]。常规检测 sdLDL-C 可用于术前筛查高危患者, 优化手术方案, 术后加强监测并及早干预, 改善患者预后。sdLDL-C 仅需外周血即可常规检测, 有一定临床应用价值。

综上, sdLDL-C 是冠心病患者 PCI 术后围术期心肌损伤的危险因素, 可作为 PMI 的预测因子; sdLDL-C 与冠心病严重程度呈正相关。本研究尚存在一些不足, 为单中心研究且纳入样本量较小, 后续将进一步扩大样本量, 联合多中心进行验证, 并将 sdLDL-C 与血脂家族内其他指标如 Lp(a)、脂蛋白相关磷脂酶 A2 等进行联合研究, 寻找 PMI 的可靠预测因子及干预靶点。

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