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冠脉 PCI 治疗后血浆脂蛋白相关磷脂酶 A2 与基质金属蛋白酶 -9 水平的变化及临床意义

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摘要 目的:探讨冠脉经皮冠状动脉介入(PCI)治疗后血浆脂蛋白相关磷脂酶 A2(LP-PLA2)与基质金属蛋白酶-9(MMP-9)水平的变化及其临床意义。**方法:**选择 150 例急性冠脉综合征(ACS)患者、128 例稳定型心绞痛(SAP)患者及 100 例健康者分为作为 ACS 组、SAP 组及对照组。比较三组入院时血浆 MMP-9、LP-PLA2 水平及 ACS 组经 PCI 治疗前后血浆 MMP-9、LP-PLA2 水平的变化。**结果:**与对照组比较,SAP 组与 ACS 组的血浆 MMP-9、LP-PLA2 水平均明显增高($P < 0.05$);与 SAP 组比较,ACS 组明显增高($P < 0.05$)。与术前比较,ACS 组术后血浆 MMP-9、LP-PLA2 水平明显降低($P < 0.05$)。MMP-9 与 LP-PLA2 在 ACS 组血浆中呈显著正相关($r=0.617, P < 0.05$),在 SAP 组与对照组中无相关性($P > 0.05$)。**结论:**冠脉病变程度越严重,血浆 MMP-9 和 LP-PLA2 水平更高;PCI 治疗后冠脉斑块趋于稳定,血浆 MMP-9 和 LP-PLA2 水平降低,且二者有相关性,提示 MMP-9 和 LP-PLA2 参与冠状动脉粥样硬化的发病与发展,且对预测 ACS 高危人群及评价疗效有一定的临床价值。

关键词:动脉粥样硬化;脂蛋白相关磷脂酶 A2;基质金属蛋白酶-9;经皮冠状动脉介入

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Changes and Clinical Significances of Plasma Lipoprotein Associated Phospholipase A2 and Matrix Metalloproteinase -9 in the Patients with Coronary Artery PCI

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ABSTRACT Objective: To analyze the difference of plasma lipoprotein associated phospholipase A2 (LP-PLA2) and matrix metalloproteinase -9 (MMP-9) levels in patients with different severity of coronary artery disease and the impact of percutaneous coronary intervention (PCI), investigating the role and clinical significance of two inflammatory factors in the occurrence and development of coronary artery disease. **Methods:** 150 patients with acute coronary syndrome (ACS), 128 patients with stable angina pectoris (SAP) and 100 healthy subjects were divided into ACS group, SAP group and control group. The plasma levels of MMP-9 and LP-PLA2 were compared between the three groups, and changes of plasma MMP-9 and LP-PLA2 levels before and after PCI treatment were compared in the ACS group. **Results:** Compared with the control group, the plasma MMP-9 and LP-PLA2 levels in the SAP and the ACS group were significantly higher ($P < 0.05$); and compared with the SAP group, those of the ACS group were significantly higher ($P < 0.05$). Compared with preoperative, the plasma MMP-9 and LP-PLA2 levels in the ACS group were significantly lower ($P < 0.05$). There was a significant positive correlation between MMP-9 and LP-PLA2 in the ACS group ($r=0.617, P < 0.05$), and no correlation in the SAP group and the control group ($P > 0.05$). **Conclusions:** Plasma MMP-9 and LP-PLA2 levels may be correlated with the severity of coronary artery disease, which have some clinical values in predicting ACS high risk population and evaluating the curative effect.

Key words: Atherosclerosis; Lipoprotein associated phospholipase A2; Matrix metalloproteinase -9; Percutaneous coronary intervention

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动脉粥样硬化是因高饱和脂肪摄入过多而引起的一种代谢性疾病,而近年研究显示慢性炎症是冠状动脉病变的高危因素,可增加动脉粥样硬化斑块的不稳定性和破裂^[1]。急性冠脉综合征(ACS)便是斑块破裂后继发血栓所致^[2-4]。基质金属蛋白酶

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-9(MMP-9)与脂蛋白相关磷脂酶 A2(LP-PLA2)是两种炎症因子,研究显示二者可通过不同机制作用于斑块,促使斑块纤维帽变薄,导致斑块不稳定、破裂及出血,从而引发急性冠脉事件^[2]。然而,MMP-9 和 LP-PLA2 在不同冠脉病变严重程度患者中是否有差异?经皮冠状动脉介入(PCI)治疗是否可影响其血浆水平?二者是否相关?对急性冠脉事件有无预测价值?这些问题目前仍不明确^[5-7]。为此,本研究通过观察不同人群血浆 MMP-9 和 LP-PLA2 水平变化,探讨了两种炎症因子对冠心病的临床价值。

1 资料和方法

1.1 一般资料

选择 2014 年 6 月到 2017 年 2 月在我院行经皮冠状动脉造影检查确诊为冠状动脉粥样硬化性心脏病的 278 患者,包括 128 例稳定型心绞痛 (SAP) 患者与 150 例急性冠脉综合征 (ACS)患者,分别作为 SAP 组和 ACS 组,诊断标准按美国心脏病学会和美国心脏病协会通过的诊断标准。排除合并严重肝肾功能不全、免疫性疾病、内分泌疾病、感染、肿瘤者。SAP 组男 76 例,女 52 例,年龄 49~79 岁,平均 63.12 ± 8.43 岁,体质指数 $25.33 \pm 0.54 \text{ kg/m}^2$;ACS 组男 87 例,女 63 例,年龄 47~77 岁,平均 61.25 ± 7.09 岁,体质指数 $26.04 \pm 0.83 \text{ kg/m}^2$ 。另外选择同期经冠脉造影排除冠心病者 100 例作为对照组,男 60 例,女 40 例,年龄 44~78 岁,平均 62.33 ± 8.67 岁,体质指数 $24.13 \pm 0.73 \text{ kg/m}^2$ 。三组的年龄、性别、体质指数等一般资料比较差异

均无统计学意义($P > 0.05$),具有可比性。

1.2 PCI 方法

仅 ACS 患者接受 PCI,术前口服阿司匹林片(江西制药有限公司,国药准字 H36020722)100 mg/d、氯吡格雷片(赛诺菲制药有限公司,国药准字 J20080090)75 mg/d。按传统技术进行 PCI 和药物洗脱支架植入,支架直径以 1:1 选择,支架长度大于病灶直径 3~5 mm。残余狭窄率 $< 20\%$,血流分级 TIMI3 级即为植入成功。术后服用氯吡格雷 12 个月以上,长期服用阿司匹林片。

1.3 观察指标

所有受试对象均在入院时采集静脉血 5 mL,抗凝,离心分离血浆,储存于 -70°C 冰箱待检。采用酶联免疫吸附试验法 (ELISA)检测 MMP-9 和 LP-PLA2 水平。除此之外,ACS 组另在 PCI 术后 4 周再检测一次。

1.4 统计学方法

采用 SPSS18.0 统计软件分析处理数据,计数资料以率表示,行 χ^2 检验;计量资料以表示,行 t 检验,相关性采用 Spearman 相关分析。以 $P < 0.05$ 表示差异有统计学意义。

2 结果

2.1 各组入院时血浆 MMP-9、LP-PLA2 水平比较

与对照组比较,SAP 组与 ACS 组的血浆 MMP-9、LP-PLA2 水平均明显增高 ($P < 0.05$);与 SAP 组比较,ACS 组血浆 MMP-9、LP-PLA2 水平明显增高($P < 0.05$),见表 1。

表 1 各组入院时血浆 MMP-9、LP-PLA2 水平比较(ng/mL)

Table 1 Comparison of the serum MMP-9, LP-PLA2 levels on admission between different groups(ng/mL)

Group	Cases	MMP-9	LP-PLA2
Control group	100	1.88 ± 0.14	264.40 ± 57.13
SAP group	128	$2.44 \pm 0.17^*$	$427.81 \pm 59.22^*$
ACS group	150	$7.41 \pm 1.30^{*#}$	$706.80 \pm 125.38^{*#}$

注:与对照组比较,* $P < 0.05$;与 SAP 组比较, $^{\#}P < 0.05$ 。

Note: Compared with the control group, * $P < 0.05$; Compared with SAP group, $^{\#}P < 0.05$.

2.2 ACS 患者 PCI 术前后血浆 MMP-9、LP-PLA2 水平比较

显降低($P < 0.05$),见表 2。

与术前比较,ACS 患者术后血浆 MMP-9、LP-PLA2 水平明

表 2 ACS 患者 PCI 术前后血浆 MMP-9、LP-PLA2 水平比较(ng/mL)

Table 2 Comparison of the plasma MMP-9, LP-PLA2 levels of ACS patients before and after PCI surgery(ng/mL)

Time	Case	MMP-9	LP-PLA2
Before surgery	150	7.41 ± 1.30	706.80 ± 125.38
After Surgery	150	$3.18 \pm 1.09^*$	$523.64 \pm 92.44^*$

注:与术前比较,* $P < 0.05$ 。

Note: Compared with before surgery, * $P < 0.05$.

2.3 血浆 MMP-9 与 LP-PLA2 水平的相关性分析

ACS 组血浆 MMP-9 与 LP-PLA2 水平呈显著正相关 ($P < 0.05$),SAP 组与对照组 MMP-9 与 LP-PLA2 水平无显著相关性 ($P > 0.05$),见表 3。

3 讨论

慢性炎症在动脉粥样硬化的发生、发展过程中有着重要作用。MMP-9 和 LP-PLA2 作为两种炎症因子与冠状动脉粥样硬

表 3 血浆 MMP-9 与 LP-PLA2 水平的相关性分析
Table 3 The correlation of plasma MMP-9 with LP-PLA2 levels

Groups	r	P
Control group	-0.001	>0.05
SAP group	0.273	>0.05
ACS group	0.617	<0.05

化的关系受到国内外的关注^[8-10]。MMP-9 为 IV 型胶原,来源于正常组织细胞、炎症细胞、肿瘤细胞等多种细胞。研究发现其在人动脉粥样硬化斑块处,特别是在易损斑块的肩部表现为过度表达,被指是促使斑块不稳定、破裂的重要因素^[11-13]。而这要归咎于它可特异性作用于基底膜,降解动脉粥样斑块纤维帽而使斑块破裂;同时还具有激活内皮细胞、炎症细胞、血管平滑肌细胞等作用^[14-16]。目前国内外研究基本已证明 MMP-9 与冠脉斑块的稳定性密切相关。既往相似研究显示 MMP-9 在冠状动脉粥样硬化性心脏病患者血浆中的水平明显高于正常者^[17-19]。本研究中,与对照组比较,SAP 患者与 ACS 患者的血浆 MMP-9 水平均明显增高,且 ACS 患者明显高于 SAP 患者,提示血浆 MMP-9 水平随冠脉病变程度的恶化而升高,可反映冠脉病变的严重程度,进一步证明了 MMP-9 与动脉粥样硬化的发病和发展密切相关。

血浆 LP-PLA2 主要来源于单核巨噬细胞,研究显示 LP-PLA2 分解氧化磷脂能产生两种更强的炎性介质——氧化型游离脂肪酸和溶血卵磷脂,可刺激多种炎症细胞因子生成,损伤动脉内皮,并促使单核巨噬细胞向动脉内膜浸润,吞噬氧化卵磷脂成泡沫细胞,加重冠脉病变程度^[20-24]。而且在蛋白酶及细胞因子的作用下,动脉粥样硬化斑块趋向于不稳定、破裂、出血,增加心血管事件的发生率^[25-27]。既往研究表明 LP-PLA2 对冠状动脉粥样硬化性心脏病有预测意义,可能与动脉粥样硬化性病变存在联系^[28]。本研究中,与对照患者比较,SAP 患者与 ACS 患者的血浆 LP-PLA2 水平均明显增高,且 ACS 患者明显高于 SAP 患者,LP-PLA2 与冠脉病变的严重程度有关。其它相似研究显示血浆 LP-PLA2 水平与 ACS 远期预后呈正相关,并且是独立于其它冠脉危险因子的预测因子^[29,30]。这些结果进一步提示 LP-PLA2 在动脉粥样硬化的发病和发展中发挥重要作用。

ACS 患者接受冠脉 PCI 手术 4 周后,血浆 MMP-9、LP-PLA2 水平明显降低,说明 PCI 手术可降低血浆 MMP-9、LP-PLA2 水平,其中机制可能为 PCI 术后冠脉病变趋于稳定,炎性因子减少,炎症细胞浸润得到改善,从而 MMP-9、LP-PLA2 分泌降低。不仅再次证明了 MMP-9、LP-PLA2 与冠状病变之间的关系,而且也可透过血浆 MMP-9、LP-PLA2 水平变化观察疗效。相关性分析显示 SAP 患者与健康者血浆 MMP-9 与 LP-PLA2 水平无显著相关性,但在 ACS 患者血浆中呈显著正相关,提示 MMP-9 和 LP-PLA2 对预测 ACS 高危人群具有一定的价值。虽然 MMP-9 与 LP-PLA2 的来源及作用机制有所差异,但从本研究分析来看,二者对冠状动脉粥样硬化性心脏病的发展有一定协同作用,由于潜在的免疫和炎症过程涉及到一个十分复杂的细胞因子网络,其中的具体机制尚需进一

步研究。

综上所述,MMP-9 和 LP-PLA2 参与冠状动脉粥样硬化的发病与发展,且可能协同作用;PCI 治疗后二者血浆水平下降,表明冠脉斑块趋于稳定;MMP-9 和 LP-PLA2 对预测 ACS 高危人群及评价疗效有一定的临床价值。

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