

# 炎症因子 CTRP1 血清水平与冠心病的研究

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**【摘要】** 目的:探讨补体 C1q 肿瘤坏死因子相关蛋白 1(CTRP1)血清水平与稳定型心绞痛(SA)和急性冠脉综合征(ACS)的关系。 方法:将 1263 例在我院接受冠状动脉造影的患者分为正常对照组( $n=396$ )、SA 组( $n=451$ )和 ACS 组( $n=416$ )。再将 ACS 组分为 ST 段抬高型心梗组(STEMI)和不稳定型心绞痛/非 ST 段抬高型心梗(UA/NSTEMI)组。采用酶联免疫吸附法(ELISA)检测血清 CTRP1 水平。 结果:ACS 组血清 CTRP1 水平明显高于其他两组,SA 组血清 CTRP1 水平显著高于正常对照组。STEMI 组血清 CTRP1 水平显著高于 UA/NSTEMI 组( $P<0.01$ )。SA 亚组分析显示,多支病变组血清 CTRP1 显著高于单支病变组。冠心病患者血清 CTRP1 水平与肿瘤坏死因子- $\alpha$ (TNF- $\alpha$ )、高敏 C 反应蛋白(hsCRP)水平呈正相关。 结论:CTRP1 可能参与冠心病发病。

**【关键词】** 急性冠脉综合征;稳定型心绞痛;补体 C1q 肿瘤坏死因子相关蛋白 1

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**Increased serum CTRP1 levels are associated with the presence and severity of coronary artery disease**

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**【Abstract】 Objective:** To analyze serum levels of C1q/TNF-related protein (CTRP) 1 in patients with stable angina (SA) and acute coronary syndrome (ACS) for potential association of CTRP1 with these diseases. **Methods:** A total of 1263 participants were included in this study, categorized as control group ( $n=396$ ), SA group ( $n=451$ ) and ACS group ( $n=416$ ). Serum levels of CTRP1 protein were analyzed using commercially available ELISA kits. **Results:** Serum CTRP1 levels were significantly elevated in patients with coronary artery disease (CAD), and were the highest in the ACS group (for all comparison,  $P<0.01$ ). This bio-measurement was further analyzed by classifying ACS patients into ST-segment elevation myocardial infarction (STEMI) and unstable angina /non- ST-segment elevation myocardial infarction (UA/NSTEMI) subgroups. As expected, STEMI patients had higher CTRP1 levels than UA/NSTEMI patients. Among the SA group, a greater serum level of CTRP1 was observed in patients with multi-vessel coronary artery disease. Moreover, CTRP1 was positively correlated with tumor necrosis factor (TNF)- $\alpha$  and high sensitivity C-reactive protein (hsCRP) levels. **Conclusion:** Serum CTRP1 levels are associated with the presence and severity of CAD, indicating that CTRP1 is involved in the pathophysiology of CAD.

**【Key words】** Acute coronary syndrome; Stable angina; CTRP1

补体 C1q 肿瘤坏死因子相关蛋白 1(CTRP1)

属于 CTRP 蛋白超家族成员,广泛参与调节机体的代谢和免疫炎症过程<sup>[1-2]</sup>。CTRP1 与心血管疾病关系密切,Jeon 等<sup>[3]</sup>发现 CTRP1 在高血压患者血清中明显升高,并通过诱导细胞色素 P450 11 $\beta$  羟化酶 2(CYP11B2)的表达而刺激醛固酮的产生。血管内

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皮损伤胶原暴露后,CTRP1 可通过阻断血管性血友病因子(vWF)与胶原结合而抑制血小板聚集<sup>[4]</sup>。CTRP1 与冠心病发病的关系仍不清楚,本研究将探讨这方面的问题。

# 1 对象与方法

## 1.1 研究对象

稳定型心绞痛(SA)和不稳定型心绞痛/非 ST 段抬高型心梗(UA/NSTEMI)的根据美国心脏病学会/美国心脏协会(ACC/AHA)2007 年诊断指南<sup>[5-6]</sup>。ST 段抬高型心梗(STEMI)的诊断根据病史、心电图、和血清心肌酶谱的动态变化,陈旧性心肌梗死的诊断根据以往明确的心肌梗死病史和特征性心电图改变。

2008 年 1 月至 2010 年 8 月在我院心内科接受冠脉造影的 1263 例患者,根据临床表现和冠脉造影结果将患者分为对照组、稳定型心绞痛(SA)组和急性冠脉综合征(ACS)组。对照组 396 例,男性 200 例,女性 196 例,平均(62.9 ± 11.1)岁;SA 组 451 例,男性 323 例,女性 128 例,平均(66.0 ± 10.2)岁;ACS 组 416 例,男性 324 例,女性 92 例,平均(63.9 ± 12.8)岁。再将 SA 组分为单支和多支病变亚组。为了避免心力衰竭对血清 CTRP1 蛋白水平的影响,排除陈旧性心肌梗死和心衰患者,同时排除严重肝肾疾病、脑卒中史、恶性肿瘤、1 个月内有创伤或手术史、心脏瓣膜病、原发性心肌病和急慢性感染患者。

## 1.2 方法

冠状动脉造影影响按标准 Judkins 法,冠脉内注射硝酸甘油防止血管痉挛。主要冠脉(包括左主干、前降支、回旋支、右冠脉)管腔狭窄≥50%诊断为冠心病,左主干狭窄≥50%视为双支病变。

采集患者清晨空腹外周静脉血(ACS 患者采集其入院 24 h 内的血),分离血清低温保存。CTRP1 蛋白试剂由 Adipobioscience 公司提供,采用双抗体夹心酶联免疫法(ELISA)测定,其批间和批内变异数分别是 4%和 8%。肿瘤坏死因子-α(TNF-α)和超敏 C 反应蛋白(hsCRP)采用双抗体夹心酶联免疫法(ELISA)测定,试剂盒由 R&D System 公司提供。

## 1.3 统计学分析

所有数据采用 SPSS 16.0 统计软件包进行统

计分析,组间比较采用单因素的方差分析,两两比较采用 post-hoc Dunnett 方法。采用 Pearson 相关分析 CTRP1 与 TNF-α 和 hsCRP 的相关性。以双侧  $P<0.05$  为差异有统计学意义。

# 2 结果

## 2.1 基线资料比较

ACS 组和 SA 组男性吸烟和高脂血症的比例显著高于正常对照组( $P<0.01$ ),ACS 组低密度脂蛋白(LDL-C)水平显著高于 SA 组和正常对照组,而 ACS 组和 SA 组高密度脂蛋白(HDL-C)水平显著低于正常对照组。两组间高血压和糖尿病的发病率无统计学差异。

## 2.2 各组血清 CTRP1、TNF-α 和 hsCRP 水平比较

ACS 组患者血清 CTRP1、TNF-α 和 hsCRP 水平显著高于 SA 组和对照组,SA 组较对照组亦显著升高(见表 1)。

表 1 各组患者血清 CTRP1、TNF-α 和 hsCRP 水平比较			
组别	CTRP1(ng/ml)	TNF-α(pg/ml)	hsCRP(mg/l)
对照组	8.27 ± 1.34	55.47 ± 25.47	4.14 ± 4.04
SA 组	9.01 ± 1.91 <sup>(1)</sup>	63.55 ± 42.14 <sup>(1)</sup>	7.27 ± 5.72 <sup>(1)</sup>
ACS 组	10.89 ± 2.54 <sup>(1)(2)</sup>	88.05 ± 51.14 <sup>(1)(2)</sup>	9.39 ± 9.19 <sup>(1)(2)</sup>

注:与对照组相比,<sup>(1)</sup> $P<0.01$ ;与 SA 组相比,<sup>(2)</sup> $P<0.01$

ACS 亚组分析显示,STEMI 组 CTRP1 为(11.20 ± 2.54) ng/ml,显著高于 UA/NSTEMI 组的(10.49 ± 2.59)ng/ml, $P=0.002$ 。进一步比较单支和多支病变组 CTRP1 水平,多支病变组为(9.28 ± 2.07) ng/ml,显著高于单支病变组的(8.67 ± 1.64) ng/ml。各组内伴或不伴 2 型糖尿病的患者血清 CTRP1 水平无统计学差异。

## 2.3 血清 CTRP1 水平与 TNF-α、hsCRP 水平的相关性分析

对 CTRP1 与炎症因子 TNF-α 和 hsCRP 进行的相关性分析,结果发现血清 CTRP1 水平与 TNF-α( $r=0.141, P<0.001$ )和 hsCRP( $r=0.104, P<0.001$ )呈正相关。

# 3 讨论

CTRP 蛋白家族属于分泌蛋白,主要来源于脂肪基质细胞,血管壁内也有较高表达水平<sup>[2,4]</sup>。CTRP 家族各成员在机体的促炎或抗炎反应中起不同作用<sup>[7-9]</sup>。CTRP1 是一种多组织分泌的促炎介

质, Kim 等<sup>[10]</sup>发现将脂多糖注入大鼠体内后, 通过 TNF- $\alpha$  和白细胞介素-1 $\beta$  (IL-1 $\beta$ ) 提高脂肪组织 CTRP1 表达。高血压患者异常增高的血管紧张素 II 促进肾上腺皮质球状带上皮细胞分泌 CTRP1, 刺激醛固酮合成<sup>[3]</sup>。

本研究发现 SA 患者血清 CTRP1 水平较正常对照组显著升高, ACS 组血清 CTRP1 水平进一步升高, 且与病变严重程度密切相关。已有研究表明 CTRP1 水平与慢性炎症相关, 并参与激活腺苷酸活化蛋白激酶 (AMPK)、丝氨酸/苏氨酸激酶 (AKT) 和 P42/44 丝裂原激活蛋白激酶 (P42/44 MAPK) 等信号通路<sup>[2,11]</sup>, 提示 CTRP1 可能作为促炎介质放大血管壁细胞炎症, 其具体作用和分子调控机制有待进一步探讨。

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