

· 临床研究 ·

血清中性粒细胞明胶酶相关脂质运载蛋白对对比剂肾病的早期预测价值

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【摘要】 目的 观察冠心病患者冠状动脉造影(CAG)及经皮冠状动脉介入(PCI)术前与术后血清中性粒细胞明胶酶相关脂质运载蛋白(NGAL)水平变化,探讨NGAL预测对比剂肾病(CIN)的价值。**方法** 回顾性分析南京医科大学第二附属医院心血管内科和急诊中心2017年4月至2018年4月行CAG和PCI术的患者136例,根据术后是否发生CIN,将患者分为CIN组(10例)和非CIN组(126例),比较2组患者术前、术后24 h和48 h血肌酐(SCr)、尿素氮(BUN)以及NGAL水平并分析NGAL预测CIN的价值。采用SPSS 22.0统计软件对数据进行分析。组间比较采用*t*检验、方差分析或 χ^2 检验。绘制受试者工作特征曲线(ROC)分析血清NGAL水平对CIN的预测价值。**结果** CIN组患者术后48 h SCr、24 h BUN、48 h BUN和24 h NGAL水平相比术前增高,差异有统计学意义($P<0.05$)。相比非CIN组患者,CIN组患者术后48 h SCr[(174.95±15.77) vs (97.69±9.33) μmol/L]、24 h BUN[(7.75±1.75) vs (5.07±1.35) mmol/L]、48 h BUN[(8.92±2.03) vs (5.17±1.31) mmol/L]、术前NGAL[(341.08±205.69) vs (186.98±83.08) ng/ml]和术后24 h NGAL[(457.68±220.69) vs (185.82±51.41) ng/ml]水平增高,差异均具有统计学意义($P<0.05$)。ROC曲线显示术后24 h NGAL水平预测CIN截断点为40.325 ng/ml,曲线下面积为0.852,灵敏度70%,特异度100%。**结论** 冠心病患者PCI和CAG术后24 h血清NGAL水平明显升高,有早期预测CIN价值。

【关键词】 中性粒细胞;脂质运载蛋白;造影剂

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Early prediction of serum level of neutrophil gelatinase-associated lipid carrier protein for contrast-induced nephropathy

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【Abstract】 Objective To observe the change of serum neutrophil gelatinase-associated lipocalin (NGAL) level before and after coronary angiography (CAG) and percutaneous coronary intervention (PCI) in patients with coronary heart disease, and to investigate its predictive value of NGAL for contrast-induced nephropathy (CIN). **Methods** A total of 136 patients who underwent CAG and PCI in the Department of Cardiology and Emergency Center of our hospital from April 2017 to April 2018 were recruited, and their clinical data were collected and retrospectively analyzed. According to the occurrence of CIN, they were assigned into CIN group ($n=10$) and non-CIN group ($n=126$). The serum creatinine (SCr), blood urea nitrogen (BUN) and NGAL levels before and at 24 h and 48 h after operation were compared between 2 groups, and the predictive value of NGAL for CIN was analyzed by receiver operating characteristic (ROC) curve. The data were analyzed by SPSS statistics 22.0. Student's *t* test, ANOVA or Chi-square test was used for comparison between 2 groups. **Results** The CIN group had significantly increased levels of 48 h SCr, 24 h BUN, 48 h BUN and 24 h NGAL than those indices before operation ($P<0.05$). Compared with the non-CIN group, the CIN group had obviously higher 48 h SCr [(174.95±15.77) vs (97.69±9.33) μmol/L], 24 h BUN [(7.75±1.75) vs (5.07±1.35) mmol/L], 48 h BUN [(8.92±2.03) vs (5.17±1.31) mmol/L], and 24 h NGAL [(457.68±220.69) vs (185.82±51.41) ng/ml] (all $P<0.05$). ROC curve showed that the cut-off value of 24 h NGAL for predicting CIN was 40.325 ng/ml, and the area under the curve was 0.852, with a sensitivity of 70% and a specificity of 100%. **Conclusion** The serum level of NGAL is significantly increased in coronary heart disease patients at 24 h after PCI and CAG, and the index shows early predictive value for CIN.

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【Key words】 neutrophil; lipocalin; contrast media

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冠心病(coronary heart disease, CHD)是动脉粥样硬化引起冠状动脉管腔狭窄或闭塞,从而导致心肌缺血、缺氧或坏死。目前针对冠心病患者,冠状动脉造影(coronary angiography, CAG)及经皮冠状动脉介入(percutaneous coronary intervention, PCI)术是诊断及治疗的重要方法,手术过程中需使用对比剂。但对比剂引起的肾损害发生率越来越高,已成为继肾毒性药物、肾灌注不足导致医源性急性肾功能衰竭的第三大病因^[1,2]。对比剂引起的急性肾功能损伤缺乏有效的早期预测手段,诊断对比剂肾病(contrast-induced nephropathy, CIN)主要依据血肌酐(serum creatinine, SCr)水平,但SCr水平受患者性别、年龄、种族、代谢药物及蛋白质摄入等影响,因此误差很大。而且SCr水平明显升高出现较晚,多在对对比剂使用48 h后,因此通过SCr水平升高来诊断CIN,有可能降低诊断准确率并造成滞后,使一些患者失去早期防治的机会^[3]。近期研究表明,中性粒细胞明胶酶相关脂质运载蛋白(neutrophil gelatinase-associated lipocalin, NGAL)是急性肾损伤(acute kidney injury, AKI)早期敏感且特异性较高的一种生物学标志物^[4],也可作为CIN的早期标志物^[5]。为此,本研究通过检测接受CAG或PCI手术患者术前、术后的血清NGAL值,以探讨该指标对早期诊断CIN的价值。

1 对象与方法

1.1 研究对象

回顾性分析南京医科大学第二附属医院心血管内科和急诊中心2017年4月至2018年4月行CAG和PCI术的患者136例,根据术后是否发生CIN,将患者分为CIN组(10例)和非CIN组(126例)。CIN诊断标准:对比剂使用3 d内血SCr水平升高至少25%或 ≥ 44 mmol/L,并排除其他导致肾损伤的病因^[6]。排除标准:(1)对比剂过敏;(2)既往有严重肝肾疾病或心力衰竭(纽约心功能分级 >3 级);(3)2周内使用过对比剂;(4)长期口服肾脏病相关药物或可能影响本试验药物;(5)急慢性炎症;(6)自身免疫性疾病、结缔组织病;(7)恶性肿瘤。所有患者均签署同意书。

1.2 介入诊疗

所有患者的介入操作均由同一组手术医师操作。术中应用对比剂有两种,一种是等渗非离子型

对比剂碘克沙醇(上海通用电气药业有限公司,批准文号J20100112),另一种是低渗非离子型对比剂碘普罗胺(拜耳先灵葆雅制药有限公司,批准文号H20030506)。

1.3 血BUN、SCr和NGAL水平检测

使用苦味酸法检测患者术前、术后24 h和48 h的SCr及血尿素氮(blood urea nitrogen, BUN)水平,使用UPT-3A型上转发光免疫分析仪(北京热景生物技术有限公司)检测患者术前、术后24 h和48 h的NGAL水平。肾脏疾病饮食改良简化(modification of diet in renal disease, MDRD)公式计算估算肾小球滤过率(estimated glomerular filtration rate, eGFR)^[7]。

1.4 统计学处理

采用SPSS 22.0统计软件对数据进行分析。计量资料用均数 $\pm$ 标准差($\bar{x} \pm s$)表示,组间比较采用 t 检验和方差分析。计数资料用例数(百分率)表示,组间比较用 χ^2 检验。绘制受试者工作特征曲线(receiver operating characteristic curve, ROC)估测血清NGAL水平对CIN的预测价值。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 2组患者基线资料比较

2组患者性别、年龄、既往病史、对比剂用量等差异无统计学意义($P > 0.05$;表1)。

2.2 2组患者BUN、SCr和NGAL水平比较

非CIN组患者术后SCr、BUN和NGAL水平相比术前差异无统计学意义($P > 0.05$)。CIN组患者术后48 h SCr、24 h BUN、48 h BUN和24 h NGAL水平相比术前增高,差异有统计学意义($P < 0.05$)。相比非CIN组患者,CIN组患者术后48 h SCr、24 h BUN、48 h BUN、术前NGAL和术后24 h NGAL水平增高,差异具有统计学意义($P < 0.05$;表2)。

2.3 血NGAL、BUN和SCr预测CIN的ROC曲线

ROC曲线显示术后24 h NGAL水平预测CIN曲线下面积(area under curve, AUC)为0.852,截断点取40.325 ng/ml时尤登指数最大,灵敏度70%,特异度100%。术后24 h SCr水平预测CIN的AUC为0.550,截断点取153.07 μ mol/L时尤登指数最大,灵敏度40%,特异度90.5%。术后48 h BUN水平预测CIN的AUC为0.990,截断点取7.27 mmol/L时尤登指数最大,灵敏度100%,特异度94.4%(图1)。

表 1 2 组患者基线资料比较

Table 1 Comparison of baseline data between two groups

Item	CIN group (n = 10)	Non-CIN group (n = 126)	t/χ ²	P value
Age(years, $\bar{x} \pm s$)	61.00±10.17	67.60±13.93	1.69	0.09
Gender(male/female, n)	6/4	86/40	0.48	0.63
History of smoking[n(%)]	4(40.00)	65(51.59)	-0.70	0.48
Hypertension[n(%)]	5(50.00)	48(38.10)	0.34	0.74
Diabetes mellitus[n(%)]	2(20.00)	31(16.67)	-0.33	0.75
Type of contrast media(iodixanol/iopromide, n)	1/9	5/121	0.89	0.38
Dosage of contrast media(ml, $\bar{x} \pm s$)	70.50±33.37	84.64±60.81	-0.73	0.47
eGFR(ml/min · 1.73 m ² , $\bar{x} \pm s$)	66.41±13.82	68.44±15.63	-0.40	0.69

CIN: contrast-induced nephropathy; eGFR: estimated glomerular filtration rate.

表 2 2 组患者术前和术后 BUN、SCr 和 NGAL 水平比较

Table 2 Comparison of level of BUN、SCr and NGAL before and after operation between two groups

Item	CIN group (n = 10)			Non-CIN group (n = 126)		
	Before operation	24 h after operation	48 h after operation	Before operation	24 h after operation	48 h after operation
SCr(μmol/L)	95.35±12.29	118.35±43.16	174.95±15.77 ^{*#}	97.46±17.50	104.47±33.71	97.69±9.33
BUN(mmol/L)	5.67±1.25	7.75±1.75 ^{*#}	8.92±2.03 ^{*#}	5.15±1.34	5.07±1.35	5.17±1.31
NGAL(ng/ml)	341.08±205.69 [#]	457.68±220.69 ^{*#}		186.98±83.08	185.82±51.41	

CIN: contrast-induced nephropathy; SCr: serum creatinine; BUN: blood urea nitrogen; NGAL: neutrophil gelatinase-associated lipocalin. Compared with before operation, ^{*}P<0.05; compared with non-CIN group, [#]P<0.05.

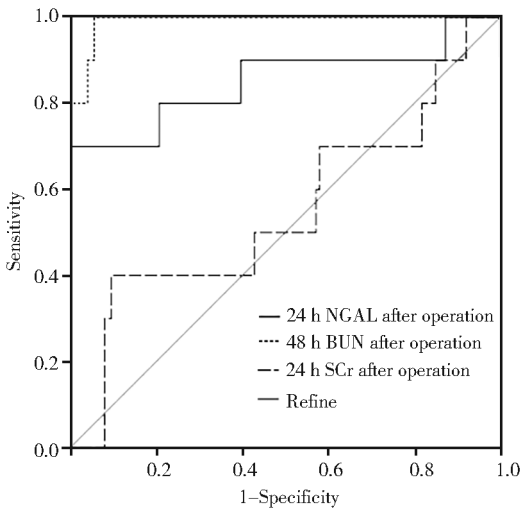


图 1 NGAL、BUN 和 SCr 预测 CIN 的 ROC 曲线

Figure 1 ROC curve of CIN predicated by NGAL、BUN and SCr

ROC: receiver operating characteristic; CIN: contrast-induced nephropathy; NGAL: neutrophil gelatinase-associated lipocalin; BUN: blood urea nitrogen; SCr: serum creatinine.

3 讨论

CIN 相关危险因素很多,国际上多采取 Mehran 评分,按照低血压、是否使用主动脉球囊反搏(intra-aortic balloon pump, IABP)、心力衰竭、SCr、年龄、贫血、糖尿病、对比剂用量 8 项进行 CIN 危险分层^[8]。近年更多研究显示,除了以上这些因素,血容量不足、低钾血症、肝功能异常、选用的对比剂种类及剂

量、合并使用可能导致肾损伤药物等均可导致患者易出现对比剂相关肾损害^[9,10]。对比剂可升高血浆渗透压,导致渗透性利尿,加重肾脏负担,减少有效循环血量,从而激活肾素-血管紧张素系统,使得缩血管物质分泌增多,引起血管平滑肌收缩而造成肾脏出现缺血和缺氧^[11]。并且离子型对比剂对肾脏肾小球管状细胞、系膜细胞等都具有毒性^[10],也可造成肾小管近段细胞线粒体活动下降,导致腺苷、次黄嘌呤等生成增加。目前,还有学者发现,对比剂可通过降低肾脏超氧化物歧化酶、过氧化氢酶的活性产生自由基,并通过自由基蓄积损害肾小管细胞^[12]。

目前临床诊断 CIN 主要依靠血 SCr 水平,但 SCr 水平高低与肾脏本身调节功能有关,通常在对对比剂导致的肾脏损害早期不会发生显著改变,因此单纯依靠 SCr 水平不能实现 CIN 的早期诊断^[13]。临床诊断 CIN 的时间窗为术后 48 h,此时血 SCr 水平已明显升高,肾脏发生严重损伤,治疗效果和预后差,因此 CIN 早期诊断预测对治疗及病情预后有明显意义,许多学者探索对 CIN 具有早期预测价值的标志物。

近几年研究显示 NGAL 是 AKI 的早期生物标志物,在损伤发生 2 h 内即可出现变化^[14]。肾脏出现轻微损伤时,SCr 升高前 1~2 d 血 NGAL 水平就开始升高,并随肾脏损伤程度加重而逐渐升高^[15]。对 128 例行 PCI 的稳定型冠心病患者研究结果显

示, CIN 患者术后 24 h NGAL 水平较非 CIN 患者明显增高, 表明术后 24 h NGA 水平对 CIN 有很好的预测价值^[16]。本研究显示 CIN 组患者术后 24 h NGAL 水平相比术前升高, 术前 NGAL 水平也较非 CIN 组患者高, 差异均具有统计学意义 ($P < 0.05$), 而 24 h SCr 水平相比术前差异无统计学意义 ($P > 0.05$), 提示 NGAL 可较 SCr 早期预示 CIN。ROC 曲线分析显示术后 24 h NGAL 预测 CIN 的灵敏度和特异度较术后 24 h SCr 高, 与以往研究结果一致。另外, 术后 48 h BUN ROC 曲线下面积尽管为 0.990, 但 BUN 水平受饮食、感染、胃肠及心脏疾病等肾外因素影响较大, 而且术后 48 h 水平才明显升高, 目前不推荐作为肾功能评估指标。

本研究有以下不足之处。(1) 我们推测尿 NGAL 水平升高峰值及 CIN 早期诊断在术后 24 h 内, 但由于本研究条件所限, 仅检测了术后 24 h 血 NGAL 水平, 如果在 24 h 内选取多个时间点留取血液标本, 检测 NGAL 水平并对结果进行分析, 可能研究结果更有意义;(2) 本研究使用北京热景生物技术有限公司 UPT-3A 型上转发光免疫分析仪检测 NGAL 水平, 其线性范围为 10~2 000 ng/ml, 检测范围较大, 检测精度有可能不佳。

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