·临床研究·

游离三碘甲状腺原氨酸和游离甲状腺素比值与急性冠脉综合征患者使用对比剂后的急性肾损伤的相关性

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【摘 要】 目的 探讨急性冠脉综合征(ACS)患者术前游离三碘甲状腺原氨酸(FT3)和游离甲状腺素(FT4)比值与使用对比剂后的急性肾损伤(PC-AKI)的相关性。**方法** 回顾性分析2016年1月至2017年12月在北部战区总医院心血管内科住院并接受经皮冠状动脉介入治疗(PCI)的10 101例ACS患者的临床资料。根据术前实验室检查结果计算FT3/FT4比值,按照FT3/FT4比值三分位进行分组,分为FT3/FT4低水平组(FT3/FT4<0.233,n=3 152),FT3/FT4中等水平组(0.233≤FT3/FT4<0.304,n=3 636)以及FT3/FT4高水平组(FT3/FT4≥0.304,n=3 313)。研究结局事件定义为ACS患者接受PCI术后PC-AKI的发生率。采用SAS 9.4软件进行数据分析。根据数据类型,组间比较分别采用单因素方差分析、*Kruskal-Wallis*检验及χ^2检验。采用限制性立方样条图分析术前FT3/FT4比值与PC-AKI的发生的相关性。**结果** 3组患者的年龄、男性比例、高血压比例、糖尿病比例、既往PCI史、吸烟情况、左室射血分数(LVEF)、血红蛋白水平、FT3及FT4水平、桡动脉入路比例、靶血管位置为前降支以及术中使用对比剂用量情况比较,差异均有统计学意义(均P<0.05)。FT3/FT4低水平、中等水平及高水平组的PC-AKI发生率分别是2.95%(93/3 152)、1.27%(46/3 636)、1.54%(51/3 313),3组间差异有统计学意义(P<0.001)。ACS患者术前FT3/FT4水平与PC-AKI发生率之间呈U型关系。以FT3/FT4比值0.305作为参考值,无论是FT3/FT4水平降低或升高,患者发生PC-AKI的风险均呈上升趋势。**结论** FT3/FT4比值与ACS患者PC-AKI的发生密切相关,无论FT3/FT4水平升高或降低,PC-AKI发生风险均呈上升趋势。

【关键词】 急性冠脉综合征;甲状腺功能;使用对比剂后急性肾损伤
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Correlation between FT3/FT4 ratio and post-contrast acute kidney injury in patients with acute coronary syndrome

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【Abstract】 Objective To investigate the correlation between preoperative free triiodothyronine (FT3) to free thyroxine (FT4) (FT3/FT4) ratio and post-contrast acute kidney injury (PC-AKI) in the patients with acute coronary syndrome (ACS). **Methods** A retrospective analysis was performed of the clinical data of 10 101 ACS patients undergoing percutaneous coronary intervention (PCI) in the General Hospital of Northern Theater Command from January 2016 to December 2017. The FT3/FT4 ratio was calculated based on the laboratory tests, and the patients were divided into three groups according to the FT3/FT4 ratio: low FT3/FT4 group (FT3/FT4<0.233, n=3 152), intermediate FT3/FT4 group (0.233≤FT3/FT4<0.304, n=3 636), and high FT3/FT4 group (FT3/FT4≥0.304, n=3 313). The endpoint of the study was defined as the incidence of PC-AKI in the ACS patients undergoing PCI. SAS 9.4 was used for statistical analysis. Depending on data type, data comparison among three groups were performed by analysis of variance, *Kruskal-Wallis* test or χ^2 test. The correlation between preoperative FT3/FT4 ratio and the occurrence of PC-AKI was analyzed using restricted cubic spline. **Results** There were statistically significant differences among the three groups in age, proportion of men, proportion of hypertension, proportion of diabetes mellitus, history of previous PCI, smoking, left ventricular ejection fraction, hemoglobin level, FT3 and FT4 levels, proportion of radial artery approach, target vessel at the anterior descending branch, and intraoperative use of contrast agent (P<0.05 for all). The incidence of PC-AKI was 2.95% (93/3 152), 1.27% (46/3 636), and 1.54% (51/3 313) in the low,

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intermediate, and high FT3/FT4 group, respectively, and the differences were statistically significant ($P<0.001$). Preoperative FT3/FT4 ratio and the incidence of PC-AKI in ACS patients showed a U-shaped relationship. Using the FT3/FT4 ratio of 0.305 as the reference value, the risk of PC-AKI tended to increase with either lower or higher FT3/FT4 ratios. **Conclusion** FT3/FT4 ratio is closely related to the occurrence of PC-AKI in ACS patients, and the risk of PC-AKI increases with either lower or higher FT3/FT4 ratios.

【Key words】 acute coronary syndrome; thyroid function; post-contrast acute kidney injury

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含碘对比剂作为常用的诊断性用药,广泛应用于急性冠脉综合征(acute coronary syndrome,ACS)的临床诊疗过程[1]。使用对比剂后的急性肾损伤(post-contrast acute kidney injury,PC-AKI)是ACS患者行经皮冠状动脉介入治疗(percutaneous coronary intervention,PCI)后常见的并发症之一,可导致肾脏功能受损及心血管相关预后不佳,甚至死亡[2,3];而PC-AKI的发病存在个体异质性,在具有高危因素的人群中更为多见[4]。因此,术前评估PC-AKI的发生风险对其防治及ACS的临床决策至关重要。研究发现,甲状腺功能与肾脏功能之间存在着一定的联系[5,6],甲状腺激素变化也可用于监测肾脏疾病的发生与发展,但甲状腺激素水平异常是否与PC-AKI的发生相关,目前尚缺乏足够的证据。基于此,本研究旨在探讨游离三碘甲状腺原氨酸(free triiodothyronine,FT3)/游离甲状腺素(free thyroxine,FT4)比值与PC-AKI之间的关系,为临床上评估PC-AKI的发生风险提供依据。

1 对象与方法

1.1 研究对象

本研究选取于2016年1月至2017年12月在北部战区总医院心血管内科住院并接受PCI治疗的10 101例ACS患者为研究对象。纳入标准:(1)诊断为ACS且接受PCI治疗;(2)术前进行甲状腺及肾脏功能实验室检查;(3)病情稳定后出院。排除标准:FT3、FT4以及肌酐(creatinine, Cr)数据缺失。根据术前甲状腺功能检验结果计算FT3/FT4比值,按照FT3/FT4比值三分位进行分组,分为FT3/FT4低水平组(FT3/FT4<0.233,n=3 152),FT3/FT4中等水平组(0.233≤FT3/FT4<0.304,n=3 636)以及FT3/FT4高水平组(FT3/FT4≥0.304,n=3 313)。本研究经北部战区总医院伦理委员会批准[伦审K(2018)35号]。

1.2 方法

收集患者的实验室检查结果,以及临床基线资料、介入治疗相关资料等。研究结局事件定义为ACS患者接受PCI术后PC-AKI的发生率。PC-AKI是指使用对比剂后48 h内出现的任何急性肾损伤,即血清Cr值较基线期水平升高≥26.5 μmol/L或达到基线期水平的1.5倍以上[7]。

1.3 统计学处理

采用SAS 9.4统计学软件对数据进行处理。符合正态分布的计量资料用均数±标准差($\bar{x}\pm s$)表示,采用单因素方差分析;非正态分布的计量资料,用中位数(四分位数间距)[$M(Q_1, Q_3)$]表示,采用*Kruskal-Wallis*检验。计数资料用例数(百分率)表示,采用χ^2检验。采用限制性立方样条图(restricted cubic spline, RCS)分析术前FT3/FT4比值与PC-AKI发生的相关性。$P<0.05$为差异有统计学意义。

2 结 果

2.1 3组患者临床基线资料比较

3组患者的年龄、男性比例以及吸烟情况比较,差异均有统计学意义(均$P<0.05$);患者合并高血压、糖尿病比例以及既往PCI比例,3组间差异均有统计学意义(均$P<0.05$);同时,3组患者的冠心病诊断、左室射血分数(left ventricular ejection fraction, LVEF)、血红蛋白水平、FT3及FT4水平、术前与术后的血清Cr及估算的肾小球滤过率(estimated glomerular filtration rate, eGFR)比较,差异均有统计学意义(均$P<0.05$)。其他一般资料比较,差异均无统计学意义(表1)。

2.2 3组患者介入资料比较

3组间桡动脉入路比例、靶血管位置为前降支、术中使用对比剂用量以及Syntax评分比较,差异均有统计学意义(均$P<0.05$);其他一般资料比较,差异均无统计学意义(表2)。

2.3 3组患者PC-AKI发生率比较

FT3/FT4低水平、中等水平及高水平患者接受PCI治疗后发生PC-AKI的事件率分别为2.95%(93/3 152)、1.27%(46/3 636)、1.54%(51/3 313),3组间差异有统计学意义($P<0.001$)。

表 1 3 组患者临床基线资料比较

Table 1 Comparison of baseline characteristics of patients among three groups

Item	Low FT3/FT4 group (n=3 152)	Intermediate FT3/FT4 group (n=3 636)	High FT3/FT4 group (n=3 313)	F/χ^2	P value
Age (years, $\bar{x}\pm s$)	62.57±10.26	60.65±10.15	59.10±10.16	94.006	<0.001
Male [n(%)]	2 167 (68.75)	2 701 (74.28)	2 504 (75.58)	43.110	<0.001
BMI (kg/m^2, $\bar{x}\pm s$)	25.90±16.68	25.70±7.04	26.06±9.04	0.846	0.429
Hypertension [n(%)]	2 051 (65.07)	2 230 (61.33)	2 002 (60.43)	16.630	<0.001
Diabetes mellitus [n(%)]	1 132 (35.91)	1 036 (28.49)	906 (27.35)	66.091	<0.001
Insulin treated diabetes mellitus [n(%)]	482 (15.29)	497 (13.67)	446 (13.46)	5.365	0.068
Prior MI [n(%)]	599 (19.00)	723 (19.88)	665 (20.07)	1.331	0.514
Prior stroke [n(%)]	434 (13.77)	435 (11.96)	402 (12.13)	5.906	0.052
Prior PCI [n(%)]	770 (24.43)	959 (26.38)	918 (27.71)	9.071	0.011
Smoking status [n(%)]				53.578	<0.001
Current smoking	1 156 (36.72)	1 529 (42.09)	1 473 (44.50)		
Smoking cessation	535 (16.99)	632 (17.40)	582 (17.58)		
Never smoking	1 457 (46.28)	1 472 (40.52)	1 255 (37.92)		
Type of coronary artery disease [n(%)]				102.823	<0.001
Unstable angina	1 669 (52.95)	2 269 (62.40)	2 119 (63.96)		
NSTEMI	588 (18.65)	580 (15.95)	442 (13.34)		
STEMI	895 (28.39)	787 (21.64)	752 (22.70)		
LVEF (%, $\bar{x}\pm s$)	57.55±9.58	59.44±8.50	59.46±8.41	56.586	<0.001
Hemoglobin (g/L, $\bar{x}\pm s$)	135.55±15.45	138.47±14.64	139.56±14.31	113.983	<0.001
FT3 (pg/ml, $\bar{x}\pm s$)	2.35±0.49	2.74±0.75	3.08±0.61	1064.213	<0.001
FT4 (ng/dl, $\bar{x}\pm s$)	1.22±0.41	1.03±0.27	0.84±0.16	1351.528	<0.001
Cr (μmol/L, $\bar{x}\pm s$)					
Preoperative	78.38±51.49	74.70±24.22	73.40±18.88	15.230	0.001
Postoperative	74.70±51.23	69.98±23.70	69.17±18.78	32.142	<0.001
eGFR [ml/(min · 1.73m^2), $\bar{x}\pm s$]					
Preoperative	94.53±31.64	98.16±24.46	100.24±24.72	36.934	<0.001
Postoperative	100.43±28.21	106.50±27.08	107.81±26.88	66.786	<0.001
eGFR<60 [ml/(min · 1.73m^2), n(%)]					
Preoperative	262 (8.31)	193 (5.31)	120 (3.62)	67.748	<0.001
Postoperative	231 (7.33)	150 (4.13)	108 (3.26)	64.363	<0.001

FT3: free triiodothyronine; FT4: free thyroxine; BMI: body mass index; MI: myocardial infarction; PCI: percutaneous coronary intervention; NSTEMI: non-ST-segment-elevation myocardial infarction; STEMI: ST-segment-elevation myocardial infarction; LVEF: left ventricular ejection fraction; Cr: creatinine; eGFR: estimated glomerular filtration rate.

表 2 3 组患者介入资料比较

Table 2 Comparison of angiographic characteristics of patients among three groups

Item	Low FT3/FT4 group (n=3 152)	Intermediate FT3/FT4 group (n=3 636)	High FT3/FT4 group (n=3 313)	$\chi^2/F/H$	P value
PPCI [n(%)]	462 (14.66)	385 (10.59)	402 (12.13)	26.037	<0.001
Radial PCI [n(%)]	2 941 (93.31)	3 444 (94.72)	3 165 (95.53)	15.867	<0.001
Treated lesions [n(%)]					
LM	268 (8.65)	325 (9.06)	270 (8.24)	1.471	0.479
LAD	1 773 (57.19)	1 991 (55.51)	1 923 (58.66)	6.999	0.030
LCX	752 (24.26)	839 (23.39)	782 (23.86)	0.696	0.706
RCA	1 169 (37.71)	1 358 (37.86)	1 173 (35.78)	3.807	0.149
Number of target vessels (n, $\bar{x}\pm s$)	1.20±0.48	1.18±0.46	1.19±0.47	2.327	0.098
Number of stents (n, $\bar{x}\pm s$)	1.78±1.08	1.75±1.03	1.75±1.06	0.468	0.626
Stent length (mm, $\bar{x}\pm s$)	47.77±32.36	47.39±31.27	46.97±32.09	0.474	0.623
Stent diameter (mm, $\bar{x}\pm s$)	3.01±0.38	3.09±2.66	3.05±0.62	1.912	0.148
Contrast agent dose [ml, $M(Q_1, Q_3)$]	160.00 (120.00, 200.00)	160.00 (120.00, 200.00)	180.00 (130.00, 220.00)	51.213	<0.001
SYNTAX score (points, $\bar{x}\pm s$)	14.88±8.59	14.46±8.91	14.25±8.31	3.458	0.032

PPCI: primary percutaneous coronary intervention; PCI: percutaneous coronary intervention; LM: left main artery; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery.

2.4 FT3/FT4水平与PC-AKI发生率的相关性分析

在校正了人口学及介入治疗情况后，采用RCS法分析结果显示：ACS患者术前FT3/FT4水平与PC-AKI发生率之间呈U型关系；以FT3/FT4比值0.305作为参考值，无论是FT3/FT4水平降低或升高，患者发生PC-AKI的风险均呈上升趋势（图1）。

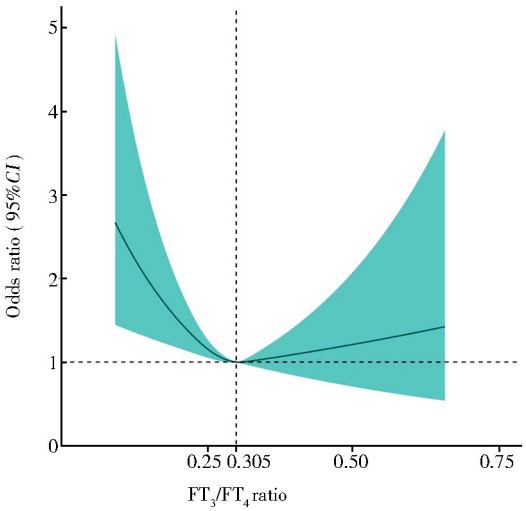

图1 FT3/FT4比值与对比剂使用后的急性肾损伤发生率的相关性

Figure 1 Correlation between FT3/FT4 ratio and incidence of PC-AKI

FT3: free triiodothyronine; FT4: free thyroxine; PC-AKI: post-contrast acute kidney injury.

3 讨 论

PC-AKI是特发于注射含碘对比剂后表现为一过性肾功能下降的综合征，其发病与对比剂的直接毒性以及肾脏血流动力学改变相关。研究表明，PC-AKI可能导致PCI术后死亡、再发性心肌梗死以及肾功能不全等不良事件的发生风险显著增加[3]。而ACS患者通常具有较高的合并症发生率，更易发生急性血流动力学障碍。因此，临床上对其PCI术后PC-AKI的预防及管理日益重视。鉴于目前尚缺乏针对PC-AKI的有效治疗措施，及时、准确地预测其发生风险仍然具有重要的临床意义。

甲状腺功能障碍影响肾脏的发育及生理功能，包括肾小球和肾小管功能，并间接影响肾血流量[8]。作为甲状腺激素的主要生理活性形式，高水平的FT4、低水平的FT3均可导致肾脏疾病的发生、病情恶化以及全因死亡风险增加[9-11]。一般认为，FT3水平变化反映的是甲状腺素的外周代谢紊乱，以致甲状腺素向三碘甲状腺原氨酸转化出现异常，因此，单一激素指标可能无法反映真实的甲状腺功能变化。一项在甲功正常的人群中进行的回顾性分析数据显示，与单独分析FT3、FT4水平相比，FT3/FT4比值与肾脏功能的相关性更强[12]。既往研究已发现低FT3水平是冠心病患者PCI术后发生PC-AKI以及心血管不良事件的独立预测危险因素[13,14]，目前尚缺乏研究报道FT3/FT4比值与PC-AKI之间的关系。

本研究结果提示，FT3/FT4比值与ACS患者PCI术后的PC-AKI发生密切相关，尤其随着FT3/FT4比值降低，PC-AKI发生风险显著升高。外周脱碘酶活性变化或可解释这一结论。既往研究证实，外周脱碘酶活性影响甲状腺素向三碘甲状腺原氨酸转化过程，其降低与肾血流量降低[15]及肾脏功能减退风险增高[12,15]相关。FT3/FT4比值与肾脏病变之间同样存在一定的联系，低FT3/FT4比值的人群其肾小管间质病变程度更为严重[16]，发生肾脏替代治疗或死亡的风险更高，因此可能更易受含碘对比剂的毒性影响。此外，本研究在高水平FT3/FT4患者中也观察到了PC-AKI发生率增加，究其原因，可能与FT3/FT4高水平的患者对比剂使用剂量更高相关。鉴于以上发现，ACS患者行PCI治疗前应关注其FT3/FT4比值水平，以便及时对治疗策略进行调整。对于FT3/FT4水平过高或过低的患者，应针对性采取减少对比剂使用剂量、选用肾毒性较低的对比剂类型以及充分水化等防治措施，进一步降低PC-AKI的发生风险。

本研究存在着一定局限性：（1）本研究为回顾性研究，不能完全排除混杂因素对结果的影响，可能存在一定的偏倚；（2）本研究未提供进一步的亚组分析，后续还需对甲状腺功能与PC-AKI的相关性进行深入分析。

综上，FT3/FT4比值与ACS患者PC-AKI的发生密切相关，无论FT3/FT4水平升高或降低，PC-AKI发生风险均呈上升趋势。因此，临床上应对FT3/FT4水平给予一定的关注，从而更好地预防PC-AKI的发生。

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