·临床研究·

心外膜脂肪体积、尿微量白蛋白/肌酐比值及血清炎症因子水平与冠状动脉病变程度分析

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【摘 要】 目的 探讨冠心病患者心外膜脂肪组织体积(EATV)、尿微量白蛋白/肌酐比值(UACR)及血清炎症因子[脂蛋白相关磷脂酶A2(Lp-PLA2)、分形趋化因子(FKN)、肿瘤坏死因子-α(TNF-α)、基质金属蛋白酶-9(MMP-9)、胰岛素样生长因子-1(IGF-1)、血清胱抑素C(Cys C)]指标水平与冠状动脉病变程度之间的关系。**方法** 入选2016年3月至2017年8月解放军总医院心血管内科收治的初诊冠心病且冠状动脉狭窄患者130例及未发现冠状动脉狭窄的非冠心病者(对照组)32例,冠状动脉CT狭窄者行冠状动脉造影明确病变,并计算冠状动脉介入与外科手术治疗间协同评估(SYNTAX)评分,根据SYNTAX评分将冠状动脉狭窄患者分为低(≤22分)、中(23~32分)、高(≥33分)3组。通过冠状动脉螺旋CT图像测算患者EATV,采用免疫比浊法及酶联免疫吸附试验检测UACR及血清炎症因子水平,分析4组患者EATV、UACR及血清炎症因子水平与冠状动脉病变的相关性。采用SPSS 17.0统计软件对数据进行分析。根据数据类型,采用单因素方差分析、卡方检验或精确概率法进行组间比较;相关性分析采用Pearson积距相关法,多因素分析采用logistic逐步回归法。**结果** 高评分组EATV、Lp-PLA2、FKN、MMP-9、Cys C及UACR水平显著高于其他3组,IGF-1水平显著高于对照组及中评分组,TNF-α水平显著高于对照组及低评分组,差异均有统计学意义($P<0.05$)。中评分组EATV、Lp-PLA2、MMP-9、TNF-α及UACR水平显著高于对照组及低评分组,IGF-1水平显著低于低评分组,FKN及Cys C水平显著高于对照组,差异均有统计学意义($P<0.05$)。低评分组EATV、IGF-1水平明显高于对照组,差异有统计学意义($P<0.05$)。经相关性分析,患者EATV($r=0.41$)、UACR($r=0.69$)、血清炎症因子Lp-PLA2($r=0.72$)、IGF-1($r=0.25$)、FKN($r=0.52$)、TNF-α($r=0.49$)、MMP-9($r=0.67$)、Cys C($r=0.15$)与SYNTAX评分均呈正相关($P<0.05$)。logistic逐步回归分析显示,IGF-1(*OR*=1.064,95% *CI* 1.024~1.106,$P=0.002$)、MMP-9(*OR*=1.049,95% *CI* 1.018~1.080,$P=0.002$)、Cys C(*OR*=797.355,95% *CI* 33.729~999.999,$P=0.001$)及EATV(*OR*=1.042,95% *CI* 1.018~1.067,$P=0.005$)为冠心病发病的危险因素。**结论** 冠心病患者的EATV越大,UACR及血浆炎症因子(Lp-PLA2、IGF-1、FKN、TNF-α、MMP-9、Cys C)水平越高,冠状动脉病变SYNTAX积分越高,冠状动脉病变程度越严重。IGF-1、MMP-9、Cys C、EATV可能是冠心病发病的危险因素。

【关键词】 冠心病;心外膜脂肪组织体积;尿微量白蛋白/肌酐比值;血清炎症因子
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Analysis on relationship of epicardial adipose tissue volume, urinary microalbumin/creatinine ratio and serum inflammatory factor levels with severity of coronary lesions

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【Abstract】 Objective To investigate the relationship of epicardial adipose tissue volume (EATV), urinary microalbumin/creatinine ratio (UACR) and serum levels of inflammatory factors, including lipoprotein-associated phospholipase A2 (Lp-PLA2), fractalkine (FKN), tumor necrosis factor-α (TNF-α), matrix metaloproteinase-9 (MMP-9), insulin-like growth factor-1 (IGF-1), and cystatin C (Cys C), with severity of coronary lesions in coronary heart disease (CHD) patients. **Methods** A total of 130 patients with freshly-diagnosed coronary artery stenosis in our department from March 2016 to August 2017 were recruited in this study. Another 32 non-CHD patients without such stenosis served as control group. The patients with coronary artery stenosis were identified by coronary angiography, and through synergy between percutaneous coronary intervention (PCI) with TAXUS stent and cardiac surgery (SYNTAX),

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their SYNTAX scores were calculated. According to the score, the patients were assigned into low (≤22), moderate (23 – 32) and high score (≥33) groups. EATV was calculated based on coronary artery spiral CT images. Latex agglutination turbidimetric immunoassay and enzyme-linked immunosorbent assay were used to determine UACR and inflammatory factor levels. The relationship of EATV, UACR and serum levels of inflammatory factors with severity of coronary lesions were analyzed in 4 groups of patients. SPSS statistics 17.0 was used to perform the statistical analysis. Student's *t* test, Chi-square test, or Fisher exact test was employed for comparison between groups based on different data types. Pearson product-moment correlation analysis was adopted for the correlation analysis, and logistic stepwise regression analysis for multiple factor analysis. **Results** The EATV, Lp-PLA2, FKN, MMP-9, Cys C levels and UACR were obviously higher in the high score group than the moderate and low score groups and control group ($P<0.05$). The high score group also had higher IGF-1 than the control and moderate score group and higher TNF-α than the control and low score group (both $P<0.05$). The moderate score group had significantly higher EATV, Lp-PLA2, MMP-9 and TNF-α levels and UACR than the control and low score group, lower IGF-1 than the low score group, but higher FKN and Cys C levels than the control group ($P<0.05$). While, the EATV and IGF-1 levels were notably higher in the low score group than control group ($P<0.05$). Correlation analysis showed that SYNTAX score was positively correlated with EATV ($r=0.41$), UACR ($r=0.69$), Lp-PLA2 ($r=0.72$), IGF-1 ($r=0.25$), FKN ($r=0.52$), TNF-α ($r=0.49$), MMP-9 ($r=0.67$) and Cys C ($r=0.15$). Logistic stepwise regression analysis indicated that IGF-1 (*OR* = 1.064, 95% *CI* 1.024 – 1.106, $P=0.002$), MMP-9 (*OR* = 1.049, 95% *CI* 1.018 – 1.080, $P=0.002$), Cys C (*OR* = 797.355, 95% *CI* 33.729 – 999.999, $P=0.001$) and EATV (*OR* = 1.042, 95% *CI* 1.018 – 1.067, $P=0.005$) were risk factors for CHD. **Conclusion** Larger EATV, higher UACR and higher serum levels of inflammatory factors (Lp-PLA2, IGF-1, FKN, TNF-α, MMP-9 and Cys C) indicate high score of SYNTAX and severe coronary lesions. IGF-1, MMP-9, Cys C and EATV might be risk factors for CHD.

【Key words】 coronary heart disease; epicardial adipose tissue volume; urinary microalbumin/creatinine ratio; serum inflammatory factors

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冠心病是威胁人类健康的重要疾病之一,随着人口老龄化,冠心病造成的社会经济负担日益加重。目前国内外研究发现心外膜脂肪组织(epicardial adipose tissue, EAT)与冠心病关系较为密切[1],亦与房颤发病、射频消融术后远期复发及血栓栓塞风险关系密切[2,3]。EAT 为一种紧贴心肌的特殊内脏脂肪,与心肌细胞共享冠状动脉供血,亦参与炎症反应[4]。有研究报道,冠心病患者 EAT 局部分泌炎症因子水平较非冠心病者高[1,4]。但目前关于冠心病患者 EAT 联合尿微量白蛋白/肌酐比值(urinary microalbumin/creatinine ratio, UACR)及血清炎症损伤标志物水平的研究尚不丰富。本研究选取疑诊冠心病入院的患者 162 例,分析心外膜脂肪组织体积(epicardial adipose tissue volume, EATV)、UACR 及炎症损伤因子与冠心病病变程度关系,希望进一步协助冠心病临床诊治。

1 对象与方法

1.1 研究对象

本研究为横断面研究,入选 2016 年 3 月至 2017 年8 月解放军总医院心血管内科收治的疑诊冠心病入院患者 162 例,年龄 37 ~ 84(56.3 ± 10.5)岁。入院后完善心脏冠状动脉 64 层螺旋 CT 检查,其中冠状动脉狭窄并行造影检查的患者 130 例(男性 75 例,女性 55 例),根据冠状动脉造影结果,即国际通用冠状动脉介入与外科手术治疗间协同评估[5](the synergy between percutaneous coronary intervention with TAXUS and cardiac surgery, SYNTAX)评分,分为低(≤22 分)、中(23 ~ 32 分)、高(≥33 分)3 组,冠状动脉未见狭窄未能确诊冠心病者 32 例(男性 20 例,女性 12 例)作为对照组。纳入标准:既往未行冠状动脉 CT 血管造影检查;无造影手术检查史、支架置入史及冠状动脉搭桥手术史。排除标准:合并感染性疾病、肝肾功能不全、急慢性心力衰竭、肿瘤及内分泌疾病患者。入院后均详细询问患者病史,告知入选研究目的。抽血检验及有必要进一步冠状动脉造影时已获得患者知情同意。

1.2 方法

收集患者基本临床资料,包括年龄、性别、体质量指数、收缩压、舒张压、心率、空腹血糖、丙氨酸氨基转移酶(alanine aminotransferase, ALT)、天门冬氨酸氨基转移酶(aspartate aminotransferase, AST)、血肌酐(serum creatinine, SCr)、尿酸(uric acid, UA)、白细胞(white blood cell, WBC)、血小板(platelets, PLT)、家族史、吸烟史、合并疾病史等。患者入院后留取次日晨尿的清洁中段尿,采用免疫比浊法检测 UACR。抽取次日清晨空腹静脉血 10 ml,于本院生化检验科严格按照说明书指定的酶联免疫吸附试验

或乳胶凝集比浊法测定血清炎症因子,包括脂蛋白相关磷脂酶 A2(lipoprotein-associated phospholipase A2, Lp-PLA2)、分形趋化因子(fractalkine, FKN)、肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)、基质金属蛋白酶-9(matrix metaloproteinase-9, MMP-9)、胰岛素样生长因子-1(insulin-like growth factor-1, IGF-1)、血清胱抑素 C(cystatin C, Cys C)。采用64层螺旋CT后处理Volumer软件(西门子,德国),人工逐层勾勒心外膜边界,设定-250~-30 HU CT值为脂肪组织,对EATV进行自动定量检测[6]。患者冠状动脉造影手术检查结果参照SYNTAX进行评分。SYNTAX评分用于评价无保护左主干病变和3支血管病变的复杂程度,首先获得病变累及的部位数目,通过SYNTAX评分计算软件根据权重系数及病变不良特征得出每个病变部位的积分,每个病变部位的积分相加得出SYNTAX积分,积分越高,反映冠状动脉病变程度越重。

1.3 统计学处理

采用SPSS 17.0统计软件对数据进行分析。计量资料以均值±标准($\bar{x}\pm s$)表示,组间比较采用单因素方差分析。计数资料以百分率表示,组间比较采用卡方检验或精确概率法。相关性分析采用Pearson积距相关法,多因素分析采用多元logistic逐步回归法。$P<0.05$为差异有统计学意义。

2 结 果

2.1 4组患者基本资料比较

4组患者SCr水平及吸烟史比例差异有统计学意义($P<0.05$);年龄、性别、体质量指数、收缩压、舒张压、心率、空腹血糖、ALT、AST、UA、WBC、PLT、冠心病家族史及合并疾病等其他参数差异无统计学意义($P>0.05$;表1)。

2.2 4组患者的EATV、UACR及血清炎症因子水平比较

高评分组EATV、Lp-PLA2、FKN、MMP-9、Cys C及UACR水平显著高于其他3组,IGF-1水平显著高于对照组及中评分组,TNF-α水平显著高于对照组及低评分组,差异均有统计学意义($P<0.05$)。中评分组EATV、Lp-PLA2、MMP-9、TNF-α及UACR水平显著高于对照组及低评分组,IGF-1水平显著低于低评分组,FKN及Cys C水平显著高于对照组,差异均有统计学意义($P<0.05$)。低评分组EATV、IGF-1水平明显高于对照组,差异有统计学意义($P<0.05$;表2)。

表1 4组患者一般临床资料比较

Table 1 Comparison of baseline data among 4 groups

Item	Control group ($n=32$)	Low score group ($n=59$)	Moderate score group ($n=41$)	High score group ($n=30$)	P value
Age(years, $\bar{x}\pm s$)	57.21±8.91	58.93±10.19	60.82±10.18	63.20±13.66	0.399
Male[n(%)]	20(62.5)	33(55.9)	24(58.5)	18(60.0)	0.264
BMI(kg/m^2, $\bar{x}\pm s$)	27.30±2.97	26.36±3.52	25.38±2.18	26.18±3.34	0.211
SBP(mmHg, $\bar{x}\pm s$)	127.54±16.81	128.21±16.82	120.41±12.61	128.80±11.89	0.083
DBP(mmHg, $\bar{x}\pm s$)	78.49±15.62	80.87±17.91	72.12±10.21	75.80±19.98	0.506
HR(times/min, $\bar{x}\pm s$)	75.21±7.67	77.04±9.88	73.12±9.42	76.00±12.65	0.346
FBG(mmol/L, $\bar{x}\pm s$)	6.01±1.36	6.17±2.62	6.44±1.14	7.03±2.14	0.117
ALT(mmol/L, $\bar{x}\pm s$)	16.54±2.13	15.08±3.14	17.12±1.35	13.37±2.16	0.449
AST(mmol/L, $\bar{x}\pm s$)	15.22±3.45	13.72±4.56	14.32±3.88	15.02±2.48	0.094
SCr(mol/L, $\bar{x}\pm s$)	81.63±16.88	87.63±13.19	90.63±10.90	91.63±14.61	0.037
UA(mol/L, $\bar{x}\pm s$)	307.17±75.52	310.71±65.37	321.17±55.38	324.95±49.45	0.248
WBC($\times10^9$/L, $\bar{x}\pm s$)	6.28±1.74	7.02±1.64	6.89±1.96	7.31±1.07	0.181
PLT($\times10^9$/L, $\bar{x}\pm s$)	187.1±13.2	193.1±31.3	206.1±17.4	178.1±23.5	0.193
Smoking[n(%)]	10(31.3)	10(17.0)	23(56.1)	19(63.3)	0.036
CHD family history[n(%)]	5(15.63)	6(10.17)	7(17.07)	8(26.67)	0.107
Complications[n(%)]					
Hypertension	10(31.25)	11(18.64)	12(47.91)	13(43.33)	0.244
DM	6(18.75)	7(11.86)	8(19.51)	9(30.00)	0.351
HLP	13(40.63)	14(23.73)	15(36.59)	16(53.33)	0.183
CVD	3(9.38)	4(6.78)	5(12.20)	6(20.00)	0.296
Arhythmia	2(6.25)	3(5.08)	4(9.76)	5(16.67)	0.246

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; FBG: fasting blood glucose; ALT: alanine aminotransferase; AST: aspartate aminotransferase; SCr: serum creatinine; UA: uric acid; WBC: white blood cell; PLT: platelets; CHD: coronary heart disease; DM: diabetes mellitus; HLP: hyperlipidemia; CVD: cerebrovascular disease. 1 mmHg=0.133 kPa

2.3 EATV、UACR 及血清炎症因子水平与 SYNTAX 评分相关性分析

Pearson 积距相关分析显示，EATV（$r=0.414$）、UACR（$r=0.69$）、血清炎症因子 Lp-PLA2（$r=0.72$）、IGF-1（$r=0.25$）、FKN（$r=0.52$）、TNF-α（$r=0.49$）、MMP-9（$r=0.67$）、Cys C（$r=0.15$）与 SYNTAX 评分之间均呈正相关（$P<0.05$）。

2.4 冠心病危险因素的 logistic 多因素回归分析

采用二分类 logistic 逐步回归法，将变量入选标准定为 0.05，剔除标准为 0.10。将 EATV、UACR 及各血清炎症指标纳入模型中作为自变量，以是否患有冠心病作为因变量，经过入选剔除，最终得到 IGF-1、MMP-9、Cys C、EATV 为冠心病的危险因素（表 3）。

3 讨 论

随着人口老龄化加速，冠心病已成为临床常见疾病，其危险因素的拓展研究一直是学科研究的重点。本研究对初诊入院的患者进行了较严格的控制，排除了既往诊治冠心病的患者，根据冠状动脉 SYNTAX 积分进行了分组，得到不同组患者的 EATV、UACR 及血清炎症因子之间的差异有统计学意义（$P<0.05$），其中高评分组 EATV、UACR 及血清炎症因子显著高于其他 3 组，中评分组 EATV、UACR 及大多炎症因子水平亦显著高于对照组及低评分组，而低评分组仅有 EATV、IGF-1 水平明显高于对照组。总体呈现出冠状动脉病变越重的患者，EATV、UACR 以及血清炎症因子水平越高，支持目前动脉粥样硬化机制倾向于慢性炎症导致的血管结构及功能异常的研究理论[7]，即动脉粥样硬化机制具有炎症损害、脂质沉积及聚集形成粥样、血小板黏附的慢性损害特点。

为进一步研究 EATV、UACR 与冠心病病变之间的关系，我们进行了上述指标与反映冠心病病变程度的 SYNTAX 评分之间的相关性分析，发现 EATV、UACR、多项血清炎症因子水平与 SYNTAX 评分间存在正相关关系（$P<0.05$），并经 logistic 回归分析得到 EATV、IGF-1、MMP-9、Cys C 均为冠心病发病的危险因素。有研究证实，EAT 与 Genisi 积分（反映冠状动脉狭窄程度量表）、冠状动脉病变支数具有相关性[7]。目前推测 EAT 在冠状动脉血管慢性损害中起到重要作用。本研究 4 组患者的 EATV 依次显著增加（$P<0.05$），表明 EATV 作为内脏脂肪的一部分紧贴心脏，可能参与心肌重构、局部炎性等反应，为心脏病变发生发展提供基础，这与国内外研究一致[1,8]。UACR 诱发血管疾病的演变涉及内皮功能障碍，包括肾微血管损害、心脑血管甚至妊娠

表 2 4 组患者 EATV、UACR 及血清炎症因子水平比较

Table 2 Comparison of EATV, UACR and serum inflammatory factors among 4 groups ($\bar{x}\pm s$)

Item	Control group ($n=32$)	Low score group ($n=59$)	Moderate score group ($n=41$)	High score group ($n=30$)
EATV（cm^3）	125.58 ± 36.81	140.15 ± 45.38 *	153.36 ± 42.24 *#	179.75 ± 38.93 *#△
Lp-PLA2（mg/L）	132.94 ± 43.83	140.94 ± 50.61	218.76 ± 80.54 *#	263.17 ± 60.79 *#△
IGF-1（μg/L）	158.12 ± 27.32	179.62 ± 35.48 *	164.37 ± 23.67#	201.23 ± 52.29 *△
FKN（μg/L）	0.78 ± 0.21	0.95 ± 0.32	1.03 ± 0.93 *	1.18 ± 0.25 *#△
MMP-9（ng/L）	294.47 ± 28.91	303.47 ± 27.92	324.47 ± 31.13 *#	347.83 ± 32.46 *#△
TNF-α（pg/L）	20.78 ± 10.54	23.87 ± 14.65	28.78 ± 15.56 *#	30.54 ± 11.87 *#
Cys C（mg/L）	0.79 ± 0.41	0.97 ± 0.34	1.12 ± 0.38 *	1.31 ± 0.57 *#△
UACR（mg/mmol）	10.73 ± 13.94	11.17 ± 10.71	20.20 ± 10.73 *#	60.41 ± 35.34 *#△

EATV: epicardial adipose tissue volume; Lp-PLA2: lipoprotein-associated phospholipase A2; IGF-1: insulin-like growth-1; FKN: fractalkine; MMP-9: matrix metaloproteinase-9; TNF-α: tumor necrosis factor-α; Cys C: cystatin C; UACR: urinary albumin/creatinine ratio. Compared with control group, * $P<0.05$; compared with low score group, # $P<0.05$; compared with milddle score group, △ $P<0.05$

表 3 影响冠心病发病的多因素 logistic 回归分析

Table 3 Multivariate logistic regression analysis of factors affecting the incidence of coronary heart disease

Variable	*B*	*SE*	*Wald*	*P* value	*OR*	95% *CI*
Constant	−35.31	7.463	15.39	0.001	1.070	1.007 − 1.137
IGF-1	0.062	0.019	10.10	0.002	1.064	1.024 − 1.106
MMP-9	0.048	0.015	9.755	0.002	1.049	1.018 − 1.080
Cys C	6.681	1.614	17.141	0.001	797.355	33.729 − 999.999
EATV	0.041	0.012	12.026	0.005	1.042	1.018 − 1.067

IGF-1: insulin-like growth-1; MMP-9: matrix metaloproteinase-9; Cys C: cystatin C; EATV: epicardial adipose tissue volume

并发疾病[9]。UACR与SYNTAX评分之间相关系数达0.69,但回归分析显示UACR并不是冠状动脉病变严重性的危险因素,这一结果不同于目前大多数研究,考虑可能与UACR为快速测量得到且计数范围较大有关,因此有待进一步研究。另有研究指出,IGF-1具有抑制炎症、抗氧化应激、抑制泡沫细胞形成的作用,可稳定冠状动脉斑块,是冠心病的保护因素[10]。而本研究结果显示其为危险因素,亦有其他研究得出此结论[11],这可能与本研究样本量小有关,有必要扩大样本量深入分析。此外,本研究得出MMP-9及Cys C为冠状动脉病变的危险因素,MMP-9相关系数(r=0.67)高于Cys C(r=0.15),但回归方程中Cys C对冠心病影响的*OR*值最大。既往研究表明,MMP-9参与降解细胞外基质(基质胶原和弹性蛋白),破坏血管形态和功能的完整性[12]。而Cys C是在早期病理状态下释放出来的,对从坏死或炎症细胞释放出来的组织蛋白酶的活性起调节作用,具有较好的敏感性[13]。考虑Cys C分泌早于MMP-9和IGF-1等因子,具有独特优势。

另一方面,本研究相关性分析发现Lp-PLA2(r=0.72)、FKN(r=0.52)、TNF-α(r=0.49)与SYNTAX积分间亦呈正相关,他们都参与了炎症的发生发展,甚至加重了炎症损伤过程,可促进新血管形成[14,15],增强单核巨噬细胞在炎症反应中的作用,导致氧化应激和内皮损伤[15]。但回归模型分析未得到支持上述指标作为冠心病危险因素的证据。相比前述危险因素,Lp-PLA2、FKN、TNF-α可能具有较广泛的炎症反应途径而特异性较低[16]。不过本研究得到三者与冠心病冠状动脉病变正性相关的结果,证实他们亦参与了血管慢性炎症损害的过程,可在以后相关基础层面研究中进一步分析。

综上,冠心病患者EATV、UACR及血清炎症因子(Lp-PLA2、IGF-1、FKN、TNF-α、MMP-9、Cys C)水平越高,冠状动脉病变SYNTAX积分就越高,冠状动脉病变程度越严重。IGF-1、MMP-9、Cys C、EATV可能为冠心病发病的危险因素,其中Cys C对冠心病的影响程度最大。

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