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在线全文

·医学影像学论坛·

‖论　著‖

“一站式”心脏CT可探查2型糖尿病患者的冠状动脉微循环缺血*

熊一嘉[1]，朱望舒[1]，凌润键亚[1]，马　健[2]，李跃华[1△]

1. 上海交通大学医学院附属第六人民医院 放射科（上海 200233）；2. 上海交通大学医学院附属第六人民医院 心内科（上海 200233）

【摘要】 目的 采用“一站式”心脏CT扫描〔冠状动脉CT血管造影（coronary computed tomography angiography, CCTA）联合动态CT心肌灌注成像（computed tomography myocardial perfusion imaging, CT-MPI）〕分析非阻塞性冠状动脉疾病（coronary artery disease, CAD）的2型糖尿病（type 2 diabetes mellitus, T2DM）与非糖尿病患者间CT心肌灌注参数的差异，并探讨糖尿病对发生冠状动脉微循环缺血的影响。**方法** 经倾向性评分匹配均衡基线水平，最终纳入非阻塞性CAD的T2DM患者92例（T2DM组）及非糖尿病患者92例（非糖尿病组），比较两组患者的临床特征、CCTA及CT-MPI结果；采用有向无环图分析各变量之间的因果关系，筛选关键混杂因素，建立多因素回归模型，校正混杂因素后评估T2DM对发生冠状动脉微循环缺血的独立影响。**结果** T2DM组与非糖尿病组间患者的年龄、性别、高血压、高血脂、吸烟史、体质量指数、胸前区症状、钙化积分、CAD-RADS评分、辐射剂量差异均无统计学意义。T2DM组患者整体及心肌各节段（基底段、中间段、心尖段）的心肌血流量平均值与非糖尿病组相比降低（$P<0.05$）；T2DM患者冠状动脉微循环缺血的发生率高于非糖尿病患者〔21.7%（20/92） vs. 5.4%（5/92）〕，$P=0.001$〕。多因素logistic回归分析表明T2DM是冠状动脉微循环缺血的独立危险因素（比值比=5.095，95%置信区间：1.753～14.805）。**结论** CCTA联合动态CT-MPI的心脏“一站式”扫描显示，非阻塞性CAD的T2DM患者整体心肌血流灌注降低，更易发生冠状动脉微循环缺血；T2DM与冠状动脉微循环缺血独立相关。

【关键词】 冠心病　微循环　心肌缺血　心肌灌注显像　2型糖尿病

Explorative Exmination of Coronary Microcirculatory Ischemia in Type 2 Diabetes Mellitus Patients With One-Stop Cardiac Computed Tomography

XIONG Yijia[1], *ZHU Wangshu*[1], *LING Runjianya*[1], *MA Jian*[2], *LI Yuehua*[1△].

1. *Department of Radiology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine*, Shanghai 200233, China; 2. *Department of Cardiology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine*, Shanghai 200233, China

△ Corresponding author, E-mail: liyuehua77@sjtu.edu.cn

【Abstract】 Objective To analyze the differences in computed tomography (CT) myocardial perfusion parameters between type 2 diabetes mellitus (T2DM) patients and nondiabetic patients diagnosed with non-obstructive coronary artery disease (CAD), using a one-stop cardiac CT scanning protocol that combines coronary CT angiography (CCTA) with dynamic CT myocardial perfusion imaging (CT-MPI). In addition, we investigated the effect of T2DM on coronary microcirculatory ischemia. **Methods** After balancing the baseline levels with propensity score matching, 92 T2DM patients (the T2DM group) and 92 nondiabetic patients (the nondiabetic group) with non-obstructive CAD were enrolled eventually. The clinical characteristics and the CCTA and CT-MPI results of the two groups were compared. A directed acyclic graph was used to analyze the causal relationships between the variables and to identify key confounding factors. A multivariable regression model was established to evaluate the independent effect of T2DM on the occurrence of coronary microcirculatory ischemia after adjusting for confounding factors. **Results** There were no statistically significant differences between the T2DM group and the nondiabetic group in terms of age, sex, hypertension, hyperlipidemia, smoking history, body mass index, chest symptoms, calcium score, CAD-reporting and data system (CAD-RADS) score, and radiation dose. In the T2DM group, the mean values of myocardial blood flow (MBF) were significantly reduced both globally and in all myocardial segments (basal, mid, and apical segments) compared to those of the nondiabetic group ($P<0.05$). Furthermore, the incidence of coronary microcirculatory ischemia in the T2DM group was significantly higher than that in the nondiabetic group (21.7% [20/92] vs. 5.4% [5/92], $P=0.01$). Multivariable logistic

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△ 通信作者，E-mail: liyuehua77@sjtu.edu.cn

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regression analysis showed that T2DM was an important independent risk factor for coronary microcirculatory ischemia (odds ratio=5.095, 95% confidence interval: 1.753-14.805). **Conclusion** According to our assessment with a one-stop cardiac CT scanning protocol combining CCTA and dynamic CT-MPI, patients with non-obstructive CAD and T2DM have reduced global MBF, which makes them more prone to coronary microcirculatory ischemia. Furthermore, T2DM is independently associated with coronary microcirculatory ischemia.

【Key words】 Coronary disease Microcirculation Myocardial ischemia Myocardial perfusion imaging Type 2 diabetes mellitus

糖尿病是当今全球面临的主要健康挑战之一，目前全世界约有5.37亿成年人患有糖尿病，预计至2045年将有约7.83亿人受到影响[1]。其中2型糖尿病(type 2 diabetes mellitus, T2DM)约占90%，并伴随着多系统的大血管及微血管的并发症[2]。研究表明[3-4]，糖尿病会导致血管内皮生长因子受体表达减少，增加内皮细胞凋亡，降低毛细血管密度；同时，糖脂代谢异常、晚期糖化终产物的形成、内皮内葡萄糖聚集、氧化应激增加及轻度炎症反应也会引发冠状动脉(冠脉)内皮功能受损，微血管硬度增加。这些病理生理变化共同促进了冠脉微循环障碍(coronary microvascular dysfunction, CMD)的发生。CMD可导致冠脉血流减少并最终引发心肌缺血[5-6]，并增加主要心脏不良事件(major adverse cardiovascular events, MACE)的风险[7]。因此，检测糖尿病患者因CMD所致的心肌缺血具有重要的临床意义。

冠脉CT血管造影(coronary computed tomography angiography, CCTA)可提供冠脉狭窄程度、钙化积分、斑块特征等定性和定量分析信息[8-9]，临床上常用于诊断阻塞性冠脉疾病[10]，但其无法评估冠脉微血管功能。CT心肌灌注成像(computed tomography myocardial perfusion imaging, CT-MPI)可定量分析心肌灌注情况，对于由大血管引发的心肌缺血的诊断效能已得到证实[11]。CT-MPI联合CCTA的心脏CT“一站式”扫描，可对冠状动脉解剖结构、心肌情况进行全方位定量评估[12]。然而，目前尚不清楚这项技术是否有助于描述糖尿病患者心肌微循环的潜在损害。

本研究通过分析动态负荷CT-MPI的灌注结果，比较非阻塞性冠状动脉疾病(coronary artery disease, CAD)的T2DM患者和非糖尿病患者间CT心肌灌注参数结果的差异，并探讨T2DM对发生冠脉微循环缺血的影响。

1 资料与方法

1.1 研究对象

连续性收集所有在2017年1月–2023年12月期间，临床怀疑心脏疾病于上海市第六人民医院CT室行CCTA联合动态负荷CT-MPI的患者。排除标准为：①有血运重建史及心肌梗死史；②阻塞性冠状动脉疾病；③原发性心肌病；④因心脏搏动及呼吸造成严重CT图像质量受损；⑤1型糖尿病患者。参考美国糖尿病协会指南[13]诊断T2DM。纳入符合标准的111例非糖尿病患者和103例T2DM患者，记录两组患者的年龄、性别、高血压、血脂异常、吸烟史、体质量指数(body mass index, BMI)及患者与心脏相关的临床症状。采用倾向性评分匹配(propensity score matching, PSM)方法，并采用最近邻法按1∶1的比例匹配两组患者后，最终纳入非阻塞性CAD的T2DM患者与非糖尿病患者各92例。具体流程图见图1。本研究方案由上海市第六人民医院伦理委员会批准(审批编号：2020-162)。

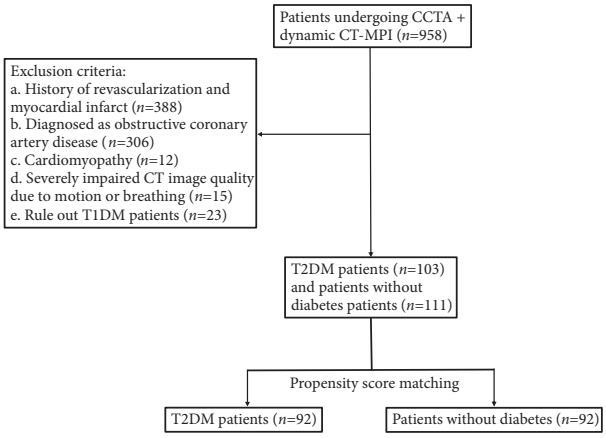

图 1 纳入研究人群的流程图

Fig 1 Flow chart of the study population enrolled

CCTA: coronary computed tomography angiography; CT-MPI: computed tomography myocardial perfusion imaging; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus.

1.2 “一站式”扫描方法

患者采用第三代双源CT(SOMATOM Force, SIEMENS Healthineers)进行检查，当天停用β受体阻滞剂，禁饮浓茶和咖啡。依次行钙化积分、动态负荷CT-MPI及CCTA扫描，范围覆盖整个左心室和冠状动脉。以160 μg/(kg·min)的速率经前臂静脉持续注入三磷酸腺苷3 min后触发灌注扫描，以6 mL/s的速率注射50 mL对比剂(碘普罗胺，碘质量浓度370 mg/mL)，使用摇篮床模式扫描动态CT-MPI，采集10 ~ 15期序列，持续32 s。采集参

数: 探测器准直96 mm×0.6 mm, 有效管电压80 kV, 球管旋转时间250 ms, 有效电流250 mA, 重建层厚0.75 mm, 重建层间距0.5 mm。随后进行CCTA扫描: CT-MPI扫描结束5 min后, 患者舌下含服硝酸甘油。经前臂静脉以4.0 ~ 5.0 mL/s的速率注射对比剂(碘普罗胺, 碘质量浓度370 mg/mL)。使用对比剂团注追踪技术监测升主动脉。采用前瞻性心电门控扫描模式, 采集时相为R-R间期, 采集参数同CT-MPI。

1.3　图像处理及分析

将所有动态扫描期相导入CT心肌灌注后处理软件(myocardial perfusion analysis, VPCT body, SIEMENS)中分析。根据美国心脏病学会17节段模型[14]勾画每个心肌节段的感兴趣区, 得到心肌血流速(myocardial blood flow, MBF)、心肌血容量(myocardial blood volume, MBV)、灌注毛细血管血容量(perfused capillary blood volume, PCBV)及达峰时间(time to peak, TTP), 并计算心肌各节段的平均值。CCTA数据重建使用平滑肌卷积核(Bv40)和第三代迭代重建技术(strength, admire3)。记录患者的钙化积分(coronary artery calcium scoring, CACS)及辐射剂量(转化系数为0.014 mSv·mGy/cm)。使用CAD-RADS评分评估患者冠脉的狭窄程度, CAD-RADS 0 ~ 2级为非阻塞性CAD[15]。以100 mL/(min·100 mL)作为临界值来区分缺血性心肌与正常心肌组织[11]。根据左心室的17段模型, 定量参数是分别从基底段(第1 ~ 6段)、中间段(第7 ~ 12段)和心尖段(第13 ~ 16段)中分析得出的平均值。在非阻塞性CAD患者中, 当至少有一个心肌段的平均MBF≤100 mL/(min·100 mL)时, 则认为该患者存在冠脉微循环缺血。

1.4　统计学方法

连续型变量不符合正态分布的用中位数和四分位数表示, 并采用Mann-Whitney *U*检验进行比较。分类变量以频率和百分比表示, 并采用卡方检验进行比较。采用Bonferroni法校正多重比较中的*P*值, 校正后*P*< 0.017为差异有统计学意义。随后, 使用R4.4.1软件中的dagitty包, 构建有向无环图(directed acyclic graph, DAG), 识别影响冠脉微循环缺血的混杂因素, 筛选多因素模型中的变量。采用多因素logistic回归模型分析各项纳入的变量与冠脉微循环缺血之间的关系, *P*< 0.05为差异有统计学意义。通过Hosmer-Lemeshow检验评估模型的拟合优度。

2　结果

2.1　基线特征

本研究共纳入214例患者, 经PSM最终纳入T2DM患者92例, 非糖尿病患者92例。两组患者的年龄、性别、高血压、高血脂、吸烟史、BMI、胸前区症状、CACS、CAD-RADS评分、辐射剂量差异均无统计学意义(表1)。

2.2　非阻塞性CAD患者CT心肌灌注参数的组间差异

在非阻塞性CAD患者中, 左室心肌基底段、中间段、

表 1　两组患者倾向性评分匹配前后基线资料特征的比较

Table 1　Comparison of baseline characteristics between the two groups of patients before and after propensity score matching

Characteristic	Before PSM			After PSM		
	Nondiabetic patients (*n*=111)	T2DM patients (*n*=103)	*P*	Nondiabetic patients (*n*=92)	T2DM patients (*n*=92)	*P*
Age/yr.*	58.00 (50.00-66.00)	64.00 (57.00-73.00)	<0.001	61.00 (54.00-67.25)	63.00 (55.75-70.00)	0.076
Male/case (%)	75 (67.6)	61 (59.2)	0.205	61 (66.3)	54 (58.7)	0.361
Hypertension/case (%)	62 (55.9)	59 (57.3)	0.833	54 (58.7)	52 (56.5)	0.881
Hyperlipidemia/case (%)	30 (27.0)	37 (35.9)	0.161	26 (28.3)	33 (35.9)	0.343
Smoking/case (%)	31 (27.9)	22 (21.4)	0.266	25 (27.2)	19 (20.7)	0.388
BMI/(kg/m^2)*	23.88 (21.89-26.12)	24.22 (21.72-27.06)	0.403	23.88 (21.85-26.06)	24.22 (21.76-27.08)	0.487
Palpitations/case (%)	9 (8.1)	12 (11.7)	0.611	11 (12.0)	5 (5.4)	0.191
Angina/case (%)	25 (22.5)	27 (26.2)	0.529	18 (19.6)	24 (26.1)	0.380
CACS*	0.00 (0.00-7.20)	0.00 (0.00-20.00)	0.077	0.00 (0.00-9.95)	0.00 (0.00-23.25)	0.101
CAD-RADS category			0.002			0.820
0	72 (64.9)	56 (54.4)		58 (63.0)	56 (60.9)	
1	2 (1.8)	15 (14.6)		2 (2.2)	4 (4.4)	
2	37 (33.3)	32 (31.1)		32 (34.8)	32 (34.8)	
Radiation dose/mSV*	7.38 (5.46-9.79)	7.22 (5.28-10.18)	0.902	7.23 (5.41-9.63)	7.65 (5.42-10.18)	0.510

T2DM: type 2 diabetes mellitus; BMI: body mass index; CACS: coronary artery calcium scoring; CAD-RADS: coronary artery disease-reporting and data system. * Median (Q1-Q3).

心尖段及整体心肌的MBF平均值在T2DM组及非糖尿病组间差异有统计学意义($P<0.017$),且T2DM组更低;MBV、PCBV在两组患者间差异均无统计学意义;基底段、中间段和整体心肌的TTP在两组间差异亦无统计学,但T2DM组心尖段TTP长于非糖尿病组($P<0.017$)(表2,图2)。T2DM组出现冠脉微循环缺血的比例高于非糖尿

表 2 T2DM患者与非糖尿病患者之间的CT心肌灌注参数比较

Table 2 Comparison of CT myocardial perfusion parameters between T2DM patients and nondiabetic patients

Parameter	Nondiabetic patients (*n*=92)	T2DM patients (*n*=92)	*P*	Corrected *P*
Basel segment*				
MBF/(mL/[min·100 mL])	162.14 (140.99-183.18)	142.41 (125.61-164.65)	<0.001	0.005
MBV/(mL/100 mL)	17.54 (15.69-18.83)	16.77 (14.82-18.45)	0.100	1.000
PCBV/(mL/100 mL)	10.43 (8.80-12.42)	9.82 (7.53-11.41)	0.031	0.492
TTP/s	10.30 (9.54-11.23)	11.07 (10.01-12.29)	0.001	0.022
Mid-ventricular segment*				
MBF/(mL/[min·100 mL])	177.23 (152.94-201.75)	158.33 (136.33-174.08)	<0.001	0.001
MBV/(mL/100 mL)	19.13 (17.20-20.39)	18.01 (16.44-19.68)	0.031	0.500
PCBV/(mL/100 mL)	11.77 (9.35-13.52)	10.42 (8.70-11.93)	0.030	0.480
TTP/s	10.07 (9.46-10.97)	10.88 (9.86-12.08)	0.001	0.021
Apical segment*				
MBF/(mL/[min·100 mL])	171.72 (150.60-197.22)	156.35 (130.88-172.06)	<0.001	0.003
MBV/(mL/100 mL)	19.06 (16.80-20.20)	17.66 (16.03-19.43)	0.036	0.570
PCBV/(mL/100 mL)	10.89 (9.11-12.77)	10.09 (8.04-11.92)	0.025	0.405
TTP/s	10.15 (9.55-11.00)	11.07 (9.93-12.35)	0.001	0.012
Globel*				
MBF/(mL/[min·100 mL])	171.04 (149.77-195.03)	153.84 (133.44-172.29)	<0.001	0.002
MBV/(mL/100 mL)	18.45 (16.53-19.96)	17.50 (15.93-19.07)	0.042	0.666
PCBV/(mL/100 mL)	11.21 (9.00-13.00)	10.13 (8.03-11.53)	0.008	0.134
TTP/s	10.16 (9.55-11.04)	10.98 (9.89-12.25)	0.001	0.020
Coronary microcirculatory ischemia/case (%)	5 (5.4)	20 (21.7)	0.001	

T2DM: type 2 diabetes mellitus; MBF: myocardial blood flow; MBV: myocardial blood volume; PCBV: perfused capillary blood volume; TTP: time to peak. Given the 17 segment model of the left ventricle, the quantitative parameters presented are the mean values derived from the analysis of the basal (segments 1-6), mid-ventricular (segments 7-12), and apical (segments 13-16) segments. Coronary microcirculation ischemia is identified when the mean MBF is found to be less than or equal to 100 mL/(min·100 mL) in at least one myocardial segment in patients with non-obstructive CAD. * Median (Q1-Q3).

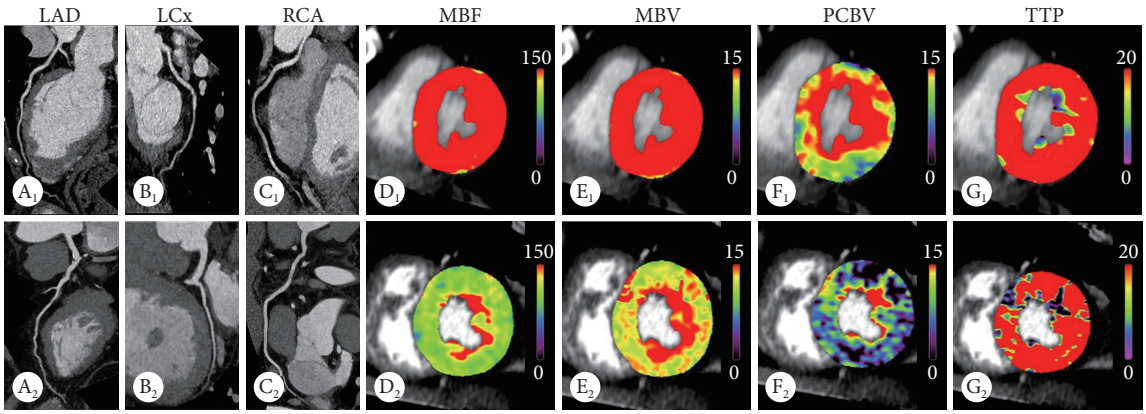

图 2 典型病例

Fig 2 Representative cases of nondiabetic patients and T2DM patients

LAD: left anterior descending artery; LCx: left circumflex artery; RCA: right coronary artery; the other abbreviations are explained in the note to Tab. 2. Case 1: A 52-year-old nondiabetic female patient presenting with chest pain of undetermined cause. A_1-C_1, curved planar reconstruction from CCTA shows no significant coronary artery stenosis; D_1-G_1, dynamic CT-MPI shows MBF ranging from approximately 157 to 280 mL/(min·100 mL), which is within the normal range. Case 2: A 66-year-old diabetic female patient presenting with chest pain of undetermined cause. A_2-C_2, CPR from CCTA shows no significant coronary artery stenosis; D_2-G_2, dynamic CT-MPI shows diffusely decreased MBF, ranging from approximately 65 to 99 mL/(min·100 mL), indicating the presence of coronary microcirculation ischemia.

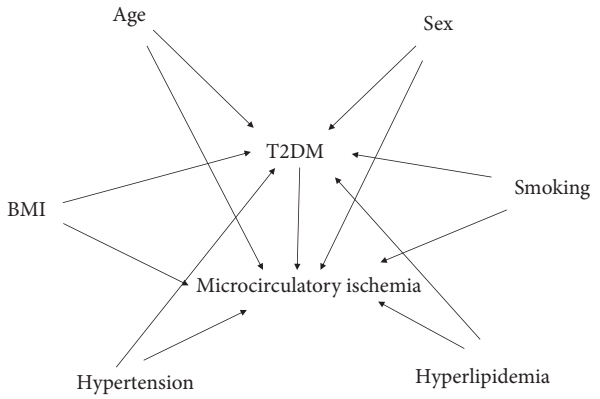

图 3 各变量因果关系的有向无环图

Fig 3 A directed acyclic graph of the causal relationships between variables

BMI: body mass index; T2DM: type 2 diabetes mellitus. The exposure is diabetes and the outcome is microvascular ischemia.

病组(21.7% vs. 5.4%, P= 0.001)(表2)。

2.3 冠脉微循环缺血影响因素多因素分析

在本研究中,根据文献回顾和临床经验绘制了暴露因素为T2DM、结局变量为冠脉微循环缺血的DAG(图3),用来筛选纳入多因素模型的混杂因素,包括年龄、性别、高血压、高血脂、吸烟、BMI。使用多因素logistic回归模型分析各自变量与冠脉微循环缺血之间的关联。模型校正了混杂因素,结果显示T2DM是冠脉微循环缺血的独立危险因素(优势比= 5.095, 95%置信区间: 1.753 ~ 14.805)(表3)。

表 3 非阻塞性CAD患者冠脉微循环缺血的多因素logistic回归分析

Table 3 Multivariate logistic regression analysis of microcirculatory ischemia in coronary arteries of patients with non-obstructive CAD

Variable	Multivariable analysis		
	Odds ratio	95% CI	*P*
T2DM	5.095	1.753-14.805	0.003
Age	1.013	0.972-1.056	0.537
Sex	1.862	0.673-5.150	0.231
Hypertension	1.513	0.557-4.105	0.417
Hyperlipidemia	0.333	0.105-1.054	0.062
Smoking	1.218	0.347-4.279	0.758
BMI	1.075	0.944-1.224	0.276

CAD: coronary artery disease; CI: confidence interval; T2DM: type 2 diabetes mellitus; BMI: body mass index.

3 讨论

越来越多的证据表明[16-17]糖尿病作为冠状动脉疾病的主要危险因素,会造成血管内皮功能和/或结构受损,影响心外膜冠状动脉及冠脉微血管系统。即使没有阻塞性CAD,冠脉微血管病和动脉粥样硬化仍在病理生理上存在联系,大多数CMD的患者仍有动脉粥样硬化的证据[18-19]。本研究通过心脏CT“一站式”扫描发现,非阻塞性CAD的T2DM患者整体心肌血流灌注降低,冠脉微循环缺血的发生率明显高于非糖尿病患者。这表明糖尿病对CMD的发展有重要影响。

由于冠脉微血管的直径较小(直径≤500 μm),传统血管造影无法可视化其解剖结构[20]。既往研究通过侵入性检查方法,如冠脉多普勒导丝或热稀释技术评估冠脉微循环情况[21],发现多达三分之二的非阻塞性CAD患者可能存在微血管功能障碍[22]。在非侵入性检测方面,正电子发射扫描(positron emission tomography, PET)被认为是CMD评估的金标准[23],它能通过量化最大MBF来测量心肌灌注储备(myocardial perfusion reserve, MPR),可评估所有冠状动脉区域[24]。另外心脏磁共振成像(cardiac magnetic resonance, CMR)也是常用的无创监测方式[25]。然而,这些方法虽然能评估心肌血流和冠脉微循环功能,但无法排除阻塞性动脉粥样硬化[20],并且检查时间长,患者配合难度大,限制了其在糖尿病患者冠脉微循环缺血中的应用。

本研究采用可同时评估冠脉解剖学和功能学的CT“一站式”扫描,观察到T2DM患者在左室心肌的多个节段及整体心肌灌注均减低,证实了糖尿病的存在对于患者心肌灌注情况的影响;此外,本研究根据既往研究[11]利用MBF以100 mL/(min·100 mL)为临界值标记微循环缺血,再通过多因素临床模型,发现在校正了多种混杂因素的情况下,T2DM仍然是患者发生微循环缺血的重要影响因素;CCTA联合CT-MPI能够综合评价冠脉解剖及心肌灌注,且该方法耗时短、经济实用,对糖尿病患者的规范化治疗有重要指导意义。

本研究局限性:研究样本量较小,可能存在数据偏倚,需进一步开展前瞻性和多中心研究以扩大样本量;未与确诊微血管功能障碍的金标准PET进行比较;CT“一站式”扫描在糖尿病阻塞性CAD患者中的价值仍需进一步验证。

综上所述,CCTA联合动态CT-MPI的心脏“一站式”扫描显示,非阻塞性CAD的T2DM患者冠脉微循环缺血发生率高于非糖尿病患者,且T2DM与冠脉微循环缺血独立相关。该扫描可有效识别糖尿病早期未出现梗阻性冠脉疾病的微循环障碍,帮助准确诊断并指导针对糖尿病患者的抗缺血治疗,从而改善缺血,降低MACE发生率。

* * *

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邮政编码：610041

联系电话：(028)85501320，(028)85500106

E-mail：scuxbyxb@scu.edu.cn

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