

·临床研究·

斑块对基于CTA虚拟计算冠状动脉血流储备分数的影响

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摘要:【目的】基于CT冠状动脉造影图像计算虚拟血流储备分数使冠状动脉病变的功能无创评估成为可能, 目前尚不清楚斑块是否会影响基于CTA虚拟计算的冠状动脉血流储备分数, 本研究以有创FFR为参考标准, 分析斑块对CT-QFR值的影响。【方法】: 回顾性研究纳入了在60 d同时接受CT冠状动脉造影(CCTA)和血流储备分数(FFR)检查的108例疑似CHD患者。通过虚拟血流计算相关软件分析CCTA图像, 获得目标血管的虚拟血流储备分数(CT-QFR)、目标血管斑块的定量及定性分析, 其中包括总斑块体积、斑块负荷、钙化斑块体积、纤维斑块体积、脂质斑块体积以及是否存在易损斑块。【结果】: 纳入108名患者的137支目标血管进行分析, 在血管水平按照CT-QFR与FFR之间的差值分为高估组(差值 >0.03 , $n=29$)、参考组($-0.03 \leq$ 差值 ≤ 0.03 , $n=88$)和低估组(差值 <-0.03 , $n=20$), 低估组(14.81)的LPV(mm^3)大于高估组(1.97, $P<0.05$)。分析显示LPV与差值呈负相关性($P<0.05$)。【结论】: 当使用CT-QFR来估算冠状动脉狭窄的血流动力学时, 脂质斑块的存在将低估血流储备分数。

关键词: 血流储备分数; 冠状动脉CT血管成像; 冠状动脉功能学; 斑块; 定量分析

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Impact of Coronary Plaque on the Precision of Computational Fractional Flow Reserve Derived from CTA

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Abstract:【Objective】The fractional flow reserve (FFR) computed from coronary computed tomographic (CT) angiograms makes it possible to noninvasively assess coronary artery disease, but the impact of plaque on FFR derived from computed tomography angiography (CTA) is still unknown. The study used invasive FFR as the reference standard to analyze the impact of plaque on coronary computed tomography angiography (CCTA)-based quantitative flow ratio (CT-QFR).【Methods】The retrospective study included 108 patients with suspected coronary heart disease (CHD) who underwent both CCTA and FFR within 60 days. CCTA images were analyzed by the software. We obtained the CT-QFR of target vessels, performed the quantitative and qualitative analyses on target vascular plaques, including total plaque volume (TPV), plaque burden, calcified plaque volume (CPV), fibrous plaque volume (FPV), lipid plaque volume (LPV), and the presence or absence of high-risk plaque.【Results】According to the difference between CT-QFR and FFR at blood vessel level, 137 target vessels of 108 patients were divided into the overestimated group (difference >0.03 , $n=29$), reference group ($-0.03 \leq$ difference ≤ 0.03 , $n=88$) and underestimated group (difference <-0.03 , $n=20$). The underestimated group (14.81mm^3) presented higher LPV than overestimated group (1.97mm^3 , $P<0.05$). There was a negative correlation between LPV and the difference ($P<0.05$).【Conclusions】When CT-QFR is used to estimate hemodynamics of coronary artery stenosis, the presence of lipid plaque may underestimate the virtual FFR.

Key words: fractional flow reserve (FFR); coronary computed tomography angiography (CCTA); coronary function; plaque; quantitative analysis

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冠状动脉狭窄和心肌缺血之间的关系极其复杂,狭窄并不一定会导致心肌缺血^[1-2]。血流储备分数(fractional flow reserve, FFR)的出现使冠状动脉功能学评估成为可能,改善了临床结果^[3-6],然而FFR的临床应用并不广泛^[7-8]。随着计算机断层扫描(computed tomography, CT)设备和计算流体动力学(computational fluid dynamics, CFD)的进展,已有研究表明基于冠状动脉CT血管成像(coronary CT angiography, CCTA)图像无创评价冠状动脉功能性狭窄的价值^[9-12],这种新兴技术可以对管腔(如流体动力学)、血管壁(如识别斑块类型、量化斑块几何信息)进行多维分析^[13],可视化、量化动脉粥样硬化病理改变及病变血管腔的血流动力学改变,诊断冠状动脉功能性缺血。该技术基于流体动力学构建血流模型,将血管管腔设定为形态固定不变的刚性管腔^[9-11, 14-15],心动周期中血管管腔的形变并未考虑在内。最近的研究表明,冠状动脉血管壁斑块“软硬”程度可能通过影响管腔形变而改变局部血流^[16-18]。基于光学相干断层扫描(optical coherence tomography, OCT)评估中度冠状动脉狭窄的血流动力学时,富含脂质斑块导致了FFR的轻微低估^[19]。目前尚不清楚基于CTA虚拟计算冠状动脉血流储备分数是否会受斑块成分的影响,本研究拟采用软件CtaPlus(Pulse Medical Technology Co, Ltd, Shanghai, China)计算冠状动脉血流储备分数(CT-QFR)并对相应血管节段的斑块成分进行量化评价,以有创FFR为参考标准,分析斑块成分对CT-QFR值的影响。

1 材料与方 法

1.1 研究对象

选取2015年3月至2022年7月于我院行CCTA检查和有创FFR检查的116例疑似冠心病(CHD)患者。纳入标准:CCTA与FFR检查时间间隔在60天内的疑似CHD患者。排除标准包括:①CT图像质量差,伴有伪影或噪声严重;②血管既往植入支架或曾行冠状动脉旁路手术(CABG)、起搏器植入等;③血管为慢性完全性闭塞(正向TIMI血流0级且闭塞时间 ≥ 3 个月的冠状动脉阻塞性病变);④完全型心肌桥。本研究经我院伦理委员会审批通过,全部参与者均免除签署知情同意书。

1.2 仪器和材料

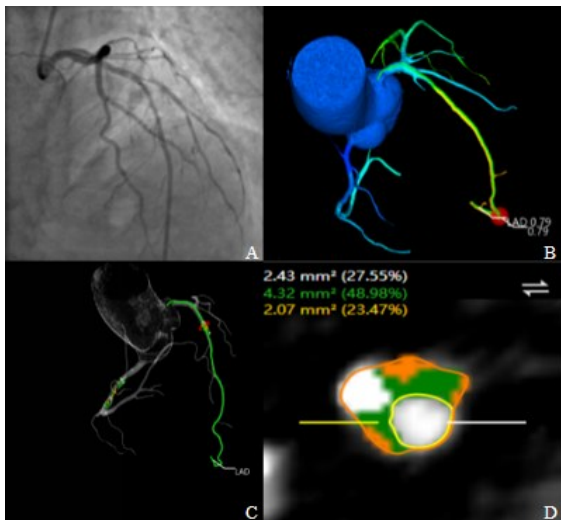
使用德国Siemens Somatom Sensation 64层和Siemens Forchheim CT进行扫描,扫描前所有患者接受屏气训练以减少呼吸运动伪影,单次屏气完成扫描并同步记录心电图。以5 mL/s的速度于肘前静脉注入55 mL对比剂(优维显370,拜耳),采用对比剂自动示踪法,于主动脉根部选择感兴趣区,触发阈值设置为100 HU。扫描为头足向自气管隆突下2 cm至膈下2 cm。扫描参数如下:探测器准直0.75 mm/0.6 mm,层厚0.75 mm/0.6 mm,管电压120~80 kV,旋转时间0.33 s/0.25 s,矩阵均为512 \times 512。

1.3 图像重建和分析

根据患者心率不同分别采用前瞻性心电触发大螺距扫描模式或回顾性心电门控螺旋扫描模式,选择运动伪影最小的期相(舒张中晚期)对图像进行重建。所有完成采集的CCTA图像均被传输到后处理站,由2名有经验且对患者FFR检查结果未知的分析人员使用CtaPlus对图像进行分析。为了分析CT-QFR分析中观察者内和观察者间的变异性,随机选择50支血管,1个月后由同一CTA分析人员和另一CTA分析人员对图像重新分析,遵循相同的标准操作程序且不知晓彼此或之前的计算结果。

首先,通过软件自动化重建出参考管腔(即发生病变前的几何模型)计算出虚拟充血流量,最后利用本课题组Tu等验证过的从成像数据中计算FFR的算法^[20-21],快速完成目标血管每个位置的定量血流储备分数计算^[12]。将目标血管远端位置与有创FFR检查中压力传感器位置相匹配,对CT-QFR值与FFR进行比较,在血管水平上按照CT-QFR和FFR之间的数值差异并分为三组:高估组CT-QFR与FFR之间的差值 > 0.03 ;参考组CT-QFR与FFR之间的差值 $\geq -0.03, \leq 0.03$;低估组CT-QFR与FFR之间的差值 < -0.03 (0.03是差值的标准差)。参考国外学者的方法使用软件将目标血管内中膜进行自动化分割^[22],对钙化斑块引起的伪影进行纠正^[23-24],随后将斑块自动化分类为钙化、纤维、脂质^[25-26],定量测定总斑块体积(total plaque volume, TPV)、纤维斑块体积(fibrous plaque volume, FPV)、脂质斑块体积(lipid plaque volume, LPV)和钙化斑块体积(calcified plaque volume, CPV),并计算总斑块负荷(目标血管中斑块体积/

血管体积 $\times 100\%$, plaque burden, PB%),如图1所示。记录基于CTA测量的最大直径狭窄率(MDS%)和最大面积狭窄率(MAS%),MDS%定义为参考管腔直径与冠脉病变最狭窄处管腔直径的差值除以参考管腔直径的比值,MAS%定义参考管腔横断面面积与冠脉病变最狭窄处管腔横断面面积的差值除以参考管腔横断面面积的比值。按照CCTA评价易损斑块(high-risk plaque feature)的特征,包括点状钙化(spotty calcium, SC)、正向重构(positive remodeling, PR)、斑块内低密度影(low HU plaque)、餐巾环征(napkin-ring sign, NRS)^[27-28],在血管节段水平判断有无易损斑块。



A: Coronary angiography shows an intermediate LAD lesion. B: Shows the CT-QFR's virtual calculation. C: Shows the reconstruction of the plaque in the coronary tree. D: shows the transverse section of the lesion.

图1 CCTA图像后处理计算CT-QFR值并自动识别斑块
Fig. 1 A representative example of CT-QFR calculation and automatic plaque characterization using software on CCTA

1.4 血流储备分数测量

采用Seldinger穿刺股动脉或桡动脉进行冠状动脉造影,随后配合指引导管将压力导丝送至目标冠状动脉进行FFR测量。行FFR测量的操作者对CCTA图像的重建分析结果未知。

1.5 统计学分析

采用SPSS 20.0版本软件进行统计分析。计量资料用均数 \pm 标准差($\bar{x} \pm s$)或中位数及四分位间距即 $M(P_{25} \sim P_{75})$ 表示,分类资料以数量和百分比($n, \%$)表示。采用Kruskal-Wallis检验或方差分析

或 T 检验来检验分析不同组间差异的统计学意义。构建单因素和多重线性回归模型,评估斑块成分和斑块特征与CT-QFR与FFR之间的差值的相关性。检验水准为 $\alpha=0.05$ 。

2 结果

排除8例患者(5例图像质量不佳,3例既往植入支架)后,本研究最终纳入108名患者137支目标血管,男77例(71.30%),女31例(28.70%),年龄范围约36~81岁,平均年龄(61.95 \pm 9.53岁)。

3组基线资料对照如表1所示,若患者存在不止一支目标血管,则分别报告各自的结果。在本研究中,108例患者中有28例患者(25.9%)出现存在不止一支目标血管的情况。目标血管的平均FFR值和CT-QFR值均为0.83, MDS%为38.10 \pm 9.90, MAS%为60.80 \pm 12.40。根据差值进行分组,高估组(>0.03)、参考组($\geq -0.03, \leq 0.03$)、低估组(< -0.03)的血管分别为29支、88支、20支;三组间是否患高血压、糖尿病、高脂血症、吸烟史的比较无统计学意义($P>0.05$)。

对44例患者的50条血管进行CT-QFR的可重复性分析。CT-QFR的观察者内和观察者间的变异性分别为0.01 \pm 0.03($P=0.556$)和-0.01 \pm 0.03($P=0.922$)。组内相关系数ICC(95%CI)分别为0.90(0.80, 0.95)和0.87(-0.73, 0.94)。

在本研究中,CT测量高估组、参考组、低估组三组MDS%分别为37.19 \pm 9.09、37.88 \pm 9.22、40.03 \pm 11.98, MAS%分别为59.73 \pm 12.03、60.57 \pm 12.06、62.69 \pm 17.15,差异均无统计学意义($P>0.05$)。高估组的PB、TPV(mm^3)、FPV(mm^3)分别为59.30 \pm 21.77、124.11 \pm 116.30、81.65(20.14~108.97),参考组的PB、TPV(mm^3)、FPV(mm^3)分别为65.93 \pm 17.45、178.93 \pm 142.72、92.59(44.55~155.34),低估组的PB、TPV(mm^3)、FPV(mm^3)分别为68.62 \pm 14.94、160.58 \pm 117.66、94.15(50.15~125.06),组间差异均无统计学意义($P>0.05$)。

高估组、参考组、低估组三组的CPV(mm^3)分别为13.66(1.03~51.19)、27.23(7.09~70.24)、0.92(0~30.70),组间差异具有统计学意义($P<0.05$)。通过对组间进行两两对比发现,参考组(27.23, $P<0.05$)的CPV(mm^3)大于低估组(0.92),组间差异具有统计学意义;高估组(13.66)的CPV(mm^3)大于低

估组(0.92)、参考组(27.23)的CPV(mm^3)大于高估组(13.66),这两组间比较无统计学意义($P>0.05$)。

高估组、参考组、低估组三组的LPV(mm^3)分别为1.97(0.14~13.58)、9.23(1.86~21.98)、14.81(5.61~57.57),组间差异具有统计学意义($P<0.05$)。通过对组间进行两两对比发现,低估组

(14.81)的LPV(mm^3)大于高估组(1.97, $P<0.05$),组间差异具有统计学意义;低估组(14.81)的LPV(mm^3)大于参考组(9.23)、参考组(9.23)的LPV(mm^3)大于高估组(1.97),这两组间比较无统计学意义($P>0.05$)。高估组、参考组、低估组三组的易损斑块发生率分别为10.3%、12.5%、10%,组间差异无统计学意义($P>0.05$)。

表1 三组基线资料对比

Table 1 Baseline data of patients in the three groups

| Vessel($n=137$) | Overestimation ($n=29$) | Reference ($n=88$) | Underestimation ($n=20$) | F/H | P |
|-------------------------|---------------------------|----------------------|----------------------------|-------|-------|
| Patient characteristics | | | | | |
| Age | 62.0±8.9 | 63.82±9.06 | 65.15±8.82 | 0.781 | 0.460 |
| Male | 22(75.9%) | 62(70.5%) | 14(70.0%) | 0.167 | 0.847 |
| Diabetes | 11(37.9%) | 33(37.5%) | 8(40.0%) | 0.021 | 0.979 |
| Hypertension | 20(69.0%) | 54(61.2%) | 8(40.0%) | 2.206 | 0.114 |
| Hyperlipidemia | 11(37.9%) | 36(40.9%) | 8(40.0%) | 0.039 | 0.961 |
| Smoking | 8(27.6%) | 37(42.0%) | 7(35.0%) | 2.009 | 0.366 |
| Plaque parameters | | | | | |
| MDS/% | 37.19±9.09 | 37.88±9.22 | 40.03±11.98 | 1.227 | 0.296 |
| MAS/% | 59.73±12.03 | 60.57±12.06 | 62.69±17.15 | 1.066 | 0.349 |
| PB | 59.30±21.77 | 65.93±17.45 | 68.62±14.94 | 1.948 | 0.147 |
| TPV/ mm^3 | 124.11±116.30 | 178.93±142.72 | 160.58±117.66 | 1.830 | 0.164 |
| CPV/ mm^3 | 13.66(1.03~51.19) | 27.23(7.09~70.24) | 0.92(0~30.70) | 6.422 | 0.04 |
| FPV/ mm^3 | 81.65(20.14~108.97) | 92.59(44.55~155.34) | 94.15(50.15~125.06) | 3.487 | 0.175 |
| LPV/ mm^3 | 1.97(0.14~13.58) | 9.23(1.86~21.98) | 14.81(5.61~57.57) | 9.361 | 0.009 |
| High-risk plaque | 3(10.3%) | 11(12.5%) | 2(10.0%) | 0.517 | 0.598 |

Data are presented as mean \pm SD or n (%) or $M(P_{25}\sim P_{75})$, patient characteristics are presented at vessel level, and for patients who have more than one vessel enrolled, results were reported separately. MDS%, maximum diameter stenosis rate derived from CCTA; MAS%, maximum area stenosis rate derived from CCTA; PB: plaque burden; TPV: total plaque volume; CPV: calcific plaque volume; FPV: fibrous plaque volume; LPV: lipidic plaque volume.

在本研究108例患者中运用线性回归模型,先进行单因素线性分析(表2),将所有单因素分析有意义的参数($P<0.2$)一起纳入多重线性回归模型,结果显示(表3)差值与LPV存在负相关($P<0.05$),LPV是CT-QFR-FFR差值的独立影响因素,LPV每增加100 mm^3 ,CT-QFR倾向于低估FFR平均值约0.042,95%CI=(-0.068, -0.015)。

3 讨论

本研究结果显示,脂质斑块负荷是CT-QFR与

FFR差值的独立影响因素。以FFR作为参考标准时,CT-QFR值的计算受斑块内脂质成分的影响,斑块中脂质斑块体积每增加100 mm^3 ,CT-QFR倾向于低估FFR平均值0.042,95%CI=(-0.068, -0.015),与国外一项研究结果基本一致^[19]。

血管腔内血流动力学不仅受到管腔狭窄的影响,还受到斑块长度和体积^[29-30]、是否偏心(斑块的一侧体积比另一侧大3倍以上)等斑块特征的影响。近期研究表明,斑块的“软硬”程度通过形变影响着相应处管腔直径的变化从而影响血流^[16-18],与刚性的纤维和钙化斑块相比,质地较软的富含脂质

表2 差值的单因素回归分析
Table 2 Single factor regression analysis of the difference

| Parameter | Estimate | 95%CI | P |
|----------------------------|----------|------------------|---------------------|
| MDS% | -0.000 3 | -0.001, 0.000 3 | 0.260 0 |
| MAS% | -0.000 2 | -0.0006, 0.000 2 | 0.341 |
| PB | -0.000 3 | -0.0006, 0 | 0.097 ¹⁾ |
| TPV/100 (mm ³) | -0.004 | -0.008, 0.001 | 0.132 ¹⁾ |
| CPV/100 (mm ³) | 0.003 | -0.008, 0.008 | 0.947 |
| FPV/100 (mm ³) | -0.008 | -0.016, 0.002 | 0.102 ¹⁾ |
| LPV/100 (mm ³) | -0.041 | -0.063, 0.019 | <0.05 ¹⁾ |
| High-risk plaque | -0.002 | -0.022, 0.017 | 0.803 |

¹⁾P<0.2; MDS%: percentage of diameters stenosis; MAS%: percentage of area stenosis; PB: plaque burden; TPV: total plaque volume; CPV: calcified plaque volume; FPV: fibrous plaque volume; LPV: lipid plaque volume.

表3 多重线性模型回归系数表
Table 3 Multiple linear model regression coefficient table

| Parameter | b | S _b | b' | t | P |
|---------------------------|----------|----------------|--------|--------|-------|
| Constant | 0.014 | 0.012 | - | 1.167 | 0.245 |
| PB | -0.000 4 | 0 | -0.002 | -0.190 | 0.985 |
| TPV/100(mm ³) | 0.002 | 0.004 2 | 0.077 | 0.504 | 0.615 |
| FPV/100(mm ³) | -0.004 | 0.007 9 | -0.078 | -0.535 | 0.593 |
| LPV/100(mm ³) | -0.042 | 0.013 | -0.309 | -3.179 | 0.002 |

PB: plaque burden; FPV: fibrotic plaque volume; LPV: lipid plaque volume.

斑块具有更大的环腔扩张和应变能力。有研究显示基于OCT评估中度冠状动脉狭窄的血流动力学时,富脂质斑块导致了其对FFR的轻微低估,这与本研究中观察到的冠状动脉生理学和粥样硬化斑块之间的关系基本相同^[19]。

在本研究CT-QFR的虚拟计算中,管腔设定为无形变的刚性管腔,相对质地较硬的钙化或纤维斑块所产生的形变轻微,局部管腔扩张幅度小,与模拟的刚性管腔类似,故不影响虚拟CT-QFR的计算。柔软的脂质斑块产生较大形变,扩大的局部血容量使有创测量的FFR值相对增高,估算的CT-QFR值会比实际FFR值偏低。

既往研究中,将横断面钙化角度>90°和厚度>1.5 mm定义为广泛钙化病变,这种病变会影响CT-QFR诊断准确性^[12],原因主要是钙化斑块导致的晕状伪影和线束硬化伪影影响了冠状动脉管腔的准确评估。Li等^[23]的研究在分析中采用了新的

图像后处理算法,结果显示其所采用的去伪影算法能够降低钙化对管腔评估的影响。本研究参考Li等^[23]的后处理算法,去除钙化伪影对管腔轮廓描绘的影响,因此在本研究结果并未显示钙化斑块负荷对CT-QFR的影响。在斑块自动分割和量化方面,本次研究采用的CtaPlus软件参考了国外学者的开发算法^[25-26],其研究显示其自动化结果与专家手工定量结果非常一致^[26],CT测量出的冠状动脉几何形状和斑块组成与虚拟组织学血管内超声(VH-IVUS)存在显著相关性^[25],基于以上算法的模型经外部研究具有很高的准确性。最近的一项研究显示,冠状动脉狭窄程度与FFR_{CT}检测冠脉缺血的诊断准确性无关^[31],这与本研究观察到的结果类似,基于CCTA图像计算得到的MDS%和MAS%在组间差异无统计意义,且对虚拟血流计算没有影响。

与CT比较,OCT评价血管壁更为精准,可明确斑块纤维帽厚度,但鉴于其有创性、价格昂贵且对

临床要求操作高,目前仍未在临床上广泛使用,并不适用于CHD的风险分层管理。CCTA作为无创方法^[32-33],是我国大规模筛查CHD的主要手段。基于CCTA的CT-QFR功能学评估鉴于其无创性及多维度分析血管病变的能力^[13],有望为CHD患者提供个性化的评估。本研究结果显示脂质成分负荷增加会影响CT-QFR的计算,同时富脂质斑块是提示斑块不稳定的重要特征,本研究结果表明,在诊断冠状动脉功能性缺血时,应将斑块特征考虑在内,以更好地对患者进行风险管理。

本研究结果补充了现有CT衍生的FFR研究方

面的不足,首次探讨影响基于CTA无创计算冠脉血流分数的因素,丰富了CT-QFR临床诊断CHD的信息,说明在评估冠脉生理指标时,不能仅局限于FFR数值,也应关注相应病变处的斑块成分,将脂质负荷考虑在内。未来的研究可着力于虚拟血流模型的优化或将粥样硬化斑块特性与冠脉功能学结合起来,优化治疗策略,以更好地对患者进行风险管理。

由于本研究为回顾性,可能会存在选择偏倚。另外,只探讨了血管水平斑块成分对FFR虚拟计算精度的影响是其不足。

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