·综 述·

无创血流储备分数测定对冠心病患者心肌缺血功能评估的临床进展

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【摘 要】 在中度病变的稳定型冠状动脉疾病(CAD)患者中,判断病变是否造成了冠状动脉远端血流动力学的显著改变(即心肌缺血),在制定临床决策中起着至关重要的作用。而在这些临界病变中,血流储备分数(FFR)测定是识别心肌缺血存在与否的金标准。近年来,随着计算机流体动力学(CFD)的发展,基于冠状动脉CT血管造影的无创性FFR(FFRCT)得以发展。本综述旨在通过阐述FFRCT的概念及应用原理,总结目前针对FFRCT技术的几项临床研究,说明其良好的诊断性能、临床实践进展、优点、局限性以及临床应用前景。

【关键词】 冠心病;血流储备分数,心肌;心肌缺血;计算机流体动力学
【中图分类号】 R541.4 【文献标志码】 A 【DOI】 10.11915/j.issn.1671-5403.2018.02.032

Clinical application of noninvasive fractional flow reserve in assessment of myocardial ischemic function in patients with coronary artery disease

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【Abstract】 For the patients with moderate-grade stable coronary artery disease (CAD), it is crucial to determine whether the lesions have significant influences on distal hemodynamics of the coronary arteries (myocardial ischemia) in the process of clinical decision-making. And in these critical conditions, fractional flow reserve (FFR) is the golden standard for identifying the presence or absence of myocardial ischemia. In recent years, with the development of computational fluid dynamics (CFD), a new technology, namely FFRCT, has been developed to calculate FFR values non-invasively based on coronary CT angiography (CCTA). In this review, we elucidated the concepts and application principles of FFRCT, and summarized several current clinical trials concerning the technique, and indicated its good diagnostic performance, clinical practice, advantages, limitations and clinical application prospects.

【Key words】 coronary artery disease; fractional flow reserve, myocardial; myocardial ischemia; computational fluid dynamics
This work was supported by the National Key R&D Program of China (2016YFC1300301).

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以往的研究表明,冠状动脉重度狭窄往往预示着心肌缺血存在。然而,随着研究的深入,人们逐渐发现冠状动脉狭窄严重程度与心肌缺血并不完全相关。有研究显示,在经冠状动脉CT血管造影(coronary computed tomographic angiography, CCTA)或侵入性冠状动脉造影(invasive coronary angiography, ICA)检查提示狭窄程度≥50%的阻塞性病变中,仅有约一半的病变导致了真正的心肌缺血[1,2];另一方面,狭窄程度≤50%的非阻塞性病变也可能会引起心肌缺血[3-5],提示冠状动脉解剖学狭窄并不一定代表功能性的心肌缺血。

冠状动脉血流储备分数(fractional flow reserve, FFR)概念的提出为冠状动脉狭窄的功能学评估开辟了新纪元,目前已成为诊断冠状动脉狭窄病变引起血流动力学异常的"金标准"[6,7]。FFR是指存在冠状动脉狭窄病变的情况下,该冠状动脉所供应区域心肌能获得的最大血流量与该区域理论上正常情况下能获得的最大血流量之比[8,9]。目前研究人员认为,引起冠状动脉血流动力学异常的FFR值在0.75~0.80之间[10-12]。FFR值<0.75的冠状动脉狭窄病变往往表现出心肌缺血的征象,而FFR值>0.80的病变则极少出现可诱导的心肌缺血征象[13,14]。

收稿日期:2017-08-12;**修回日期**:2017-09-11
基金项目:国家重点研发计划项目(2016YFC1300301)
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然而,FFR 测定需要使用压力测定导丝,具有有创性、手术费用高、风险较高及辐射量大等缺点,因而不能成为诊断心肌缺血的常规检测。近年来,随着计算机流体动力学(computational fluid dynamics, CFD)技术的发展,衍生出了一种基于 CCTA 的无创性 FFR(fractional flow reserve derived from coronary computed tomographic angiography, FFRCT)测定技术,相比经导管的有创 FFR 测定,FFRCT 测定具有无创、经济、低风险、低辐射等优点。本文就 FFRCT 的基本概念、原理、临床研究进展、优缺点及应用前景作一综述。

1 概念及原理

1.1 概念

基于冠状动脉 CTA 图像,采用 CFD 的方法模拟冠状动脉狭窄在静息及药物负荷状态下的血流动力学状态,通过该无创方法计算出的 FFR 值即为 FFRCT。

1.2 原理

随着 CFD 技术的发展,计算机可以通过 CCTA 数据模拟出冠状动脉的解剖模型和血液流体动力学模型。基于图像的血流模型的发展,使得在真实患者的特定模型中分割建立搏动的冠状动脉血流和压力模型成为可能;而且通过该模型,我们可以模拟出冠状动脉树的入口、出口边界条件,并能模拟出注射腺苷后的最大充血状态。根据既往研究,冠状动脉内血流状态遵循流体动力学物理规律,因此可以根据计算机建立的冠状动脉树模型和获取的边界条件,计算整个冠状动脉树的流体控制方程。最后,创建一个可以显示冠状动脉血液流速及压力的三维冠状动脉树模型,计算出各个点的 FFR 值[15]。

2 临床研究及进展

尽管 FFRCT 技术日益完善,临床应用前景良好,但是仍需在严格的临床试验中以有创 FFR 为“金标准”,对其临床有效性进行评估。无论是从目前著名的多中心大型临床研究,还是近期的一些单中心研究来看,FFRCT 在识别心肌缺血方面均显示出良好的诊断性能。

2.1 多中心临床研究

关于 FFRCT,目前国际上著名的多中心大型前瞻性临床研究包括 DISCOVER-FLOW 研究[16]、DeFACTO 研究[17,18]、NXT 研究[19],以及 PLATFORM 研究[20]。其中前三者均以有创 FFR 为参考标准,是评价 FFRCT 诊断价值的临床研究;后者则是首次评估 FFRCT 检查指导临床决策的准确性和临床预后效果的队列研究。

DISCOVER-FLOW 研究、DeFACTO 研究和 NXT 研究纳入的研究对象主要是临床确诊或疑诊的成年冠状动脉疾病(coronary artery disease, CAD)患者,并在 60 d 内先后进行了 CCTA、ICA 和 FFR 检查。研究结果显示,无论是以靶血管、还是以患者为研究对象进行分析,FFRCT 检查结果与 FFR 结果均呈现出良好的正相关性,且在诊断敏感性、特异性、阳性预测值、阴性预测值和准确性方面,FFRCT 较 CCTA 均有明显提升;从各个研究的受试者工作特征(receiver operating characteristic, ROC)曲线分析来看,FFRCT 的曲线下面积(area under the curve, AUC)均显示出其在识别患者缺血方面良好的诊断性能(表 1)。值得一提的是,NXT 研究纳入了更多的中度病变患者,使用了更加自动化的软件版本,并且严格按照指南加强了 β - 受体阻滞剂以及硝酸盐类药物的使用[21,22],这表明 FFRCT 检查在中度 CAD 患者中的应用前景也良好。另外,NXT 研究中的一项亚组分析表明[23],两种检查技术具有高度的可重复性。

PLATFORM 研究是首次评估 FFRCT 临床应用效果的连续性队列研究。研究结果显示,在由 FFRCT 指导的原计划行 ICA 的受试者中,有 61% 避免了有创检查,且取消 ICA 的受试者在 1 年随访中没有遭遇不良事件[24]。此外,使用 CCTA 联合 FFRCT 的诊断策略使得通过 ICA 检查显示非梗阻性疾病的发病率减少了 83%,且该策略在减少医疗保健成本的同时能够提高患者生活质量[20,24,25]。

2.2 近期的单中心临床研究

传统的 FFRCT 操作及计算需要复杂地几何建模和高强度地血流分析计算过程,这往往需要由与患者进行 CCTA 检查地点异地的超级计算机来完成。近期,伴随着一种新型的、计算强度较低的冠状动脉降阶模型出现,使得计算机断层扫描血流储备分数(computed tomography fractional flow reserve, CT-FFR)值的计算在现场即可实现。目前,已经有一些研究者通过单中心临床研究[26-29],验证了使用该新型方法进行现场 CT-FFR 操作的准确性和可靠性。从这些研究结果中可以看出,这种新型算法在显著提高 CT-FFR 计算效率的同时,仍然保持了其在识别心肌缺血病变方面良好的诊断性能(表 2)。

3 优缺点

由于 FFRCT 值是在基于 CCTA 图像的基础上运用CFD方法分析计算出来的,所以FFRCT不仅

表1 著名的FFRCT多中心临床研究

Table 1 Well-known multicenter clinical studies of FFRCT (%)

Item	Accuracy (95% *CI*)	Sensitivity (95% *CI*)	Specificity (95% *CI*)	PPV (95% *CI*)	NPV (95% *CI*)	AUC (95% *CI*)
DISCOVER-FLOW[16]						
Vessels(n=159)						
FFRCT	84(78-90)	88(77-95)	82(73-89)	74(62-84)	92(85-97)	0.90
CCTA	59(50-66)	91(81-97)	40(30-50)	47(37-56)	89(76-96)	0.75
Patients(n=103)						
FFRCT	87(79-93)	93(82-98)	82(68-91)	85(73-93)	91(78-98)	0.92
CCTA	61(51-71)	94(85-99)	25(13-39)	58(47-68)	80(52-96)	0.70
DeFACTO[18]						
Patients(n=252)						
FFRCT	73(67-78)	90(84-95)	54(46-83)	67(60-74)	84(74-90)	0.81
CCTA	64(58-70)	84(77-90)	42(34-51)	61(53-67)	72(61-81)	0.68
NXT[19]						
Vessels(n=484)						
FFRCT	86(83-89)	84(75-89)	86(82-89)	61(53-69)	95(93-97)	0.93(0.91-0.95)
CCTA	65(61-69)	83(74-89)	60(56-65)	33(27-39)	92(88-95)	0.79(0.74-0.84)
ICA	82(79-86)	55(45-65)	90(86-93)	58(48-68)	88(85-92)	
Patients(n=254)						
FFRCT	81(76-85)	86(77-92)	79(72-84)	65(56-74)	93(87-96)	0.90(0.87-0.94)
CCTA	53(47-57)	94(86-97)	34(27-41)	40(33-47)	92(83-97)	0.81(0.76-0.87)
ICA	77(71-82)	64(53-74)	83(77-88)	63(52-73)	83(77-89)	

FFRCT: fractional flow reserve derived from coronary computed tomographic angiography; CCTA: coronary computed tomographic angiography; ICA: invasive coronary angiography; PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve; CI: confidence interval

表2 现场CT-FFR的单中心临床研究

Table 2 Single-center clinical studies of on-site CT-FFR (%)

Item	Accuracy (95% *CI*)	Sensitivity (95% *CI*)	Specificity (95% *CI*)	PPV (95% *CI*)	NPV (95% *CI*)	AUC (95% *CI*)
Matthias Renker, *et al*[26]						
Vessels(n=67)						
CT-FFR		85(62-97)	85(72-94)	71(49-87)	93(81-98)	0.92
CCTA		90(68-98)	34(21-49)	37(23-52)	89(65-98)	0.72
Patients(n=53)						
CT-FFR		94(70-99)	84(68-94)	71(48-89)	97(84-99)	0.91
CCTA		94(70-99)	32(18-50)	38(23-54)	92(64-99)	0.78
Adriaan Coenen, *et al*[27]						
Vessels(n=189)						
CT-FFR	75(68-81)	88(78-94)	65(55-74)	65(55-74)	88(79-94)	0.83
CCTA	56(49-63)	81(71-89)	38(29-47)	49(40-58)	73(60-84)	0.64
Brian S. Ko, *et al*[28]						
Vessels(n=58)						
CT-FFR	83.9	78(52-93)	87(71-95)	74(49-90)	89(74-96)	0.88(0.76-1.00)
CCTA	77.6	79(54-93)	74(58-86)	60(39-78)	88(71-96)	0.77(0.65-0.80)
QCA	69.0	47(25-71)	80(63-90)	53(29-76)	76(59-87)	0.67(0.52-0.83)
ICA	65.5	90(66-98)	54(37-70)	49(32-66)	91(71-99)	0.82(0.71-0.94)

CT-FFR: computed tomography fractional flow reserve; CCTA: coronary computed tomography angiography; ICA: invasive coronary angiography; QCA: quantitative coronary angiography; PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve; CI: confidence interval

具有CCTA无创、安全、快速、经济等优点,而且FFRCT可提供整个冠状动脉生理功能学方面的信息。从上述多中心和单中心临床研究中也可以发现,FFRCT与FFR有高度相关性,在识别心肌缺血病变方面有较高的准确性。

FFRCT技术本身也存在一定的局限性。(1)高质量的CCTA图像数据是获得准确FFRCT值的关键,图像质量的好坏程度直接影响FFRCT值的准确性[30,31]。(2)过高的冠状动脉钙化积分(coronary artery calcium score,CACS)也会降低FFRCT的准确

性[32]。(3)如今 FFRCT 技术尚未常规应用于临床实践。(4)对于 FFR 值在“灰度值(0.75 ~ 0.80)”范围内的患者,FFRCT 的诊断性能欠佳[33]。(5)在微循环障碍的患者中,通过 FFRCT 计算往往会错误地估计病变远端的实际 FFR 值[15]。

4 应用前景

较之核素心肌显像等其他无创性心肌缺血评估方法[34],FFRCT 有着其不可比拟的优势。尽管目前 FFRCT 在诊断急性冠脉综合征(acute coronary syndrome, ACS)、冠状动脉旁路移植(coronary artery bypass graft, CABG)术后、经皮冠状动脉介入(percutaneous coronary intervention, PCI)术后的应用情况仍然是未知的,相信随着 CFD 技术的发展,通过计算机模拟 PCI 术后或 CABG 术后患者的血流模型终将成为可能。Chinnaiyan 等[35]发起了一项国际性多中心前瞻性临床研究(Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care, ADVANCE),该研究计划自 2015 年 7 月起累计纳入 5000 例稳定型心绞痛患者,预计 2021 年完成,旨在确定 FFRCT/CCTA 联合诊断策略能否显著改变稳定型心绞痛患者的管理方案。

诸如外周动脉、脑动脉、肾动脉等其他血管也有使用 FFRCT 技术评估血流动力学生理功能状态的可能性[15]。相信随着 FFRCT 技术的日趋成熟和标准化,再加上充分的临床研究证据,应用 FFRCT 技术指导临床医师选择相应管理策略指日可待[36]。

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(编辑: 吕青远)