·综　　述·

冠状动脉功能学评价指标在经皮冠状动脉介入术中的应用进展

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［**摘要**］ 近年来，冠状动脉功能学评价指标已用于评价病变血管生理功能、判断病变严重程度进而指导冠状动脉粥样硬化性心脏病(CHD)患者的血运重建。血流储备分数(FFR)作为一种有创的功能学指标，其有效性已被大量文献所证实，但因其具有一定局限性，因而在FFR的基础上产生了瞬时无波形比值(iFR)、定量血流分数(QFR)等多种新型功能学评价指标。这些功能学评价指标各具特色，尽管尚未在临床上广泛应用，但对冠心病患者的血运重建具有一定的评估价值。该文主要对冠状动脉功能学评价指标的特点，FFR、iFR和QFR这三类功能学评价指标的诊断及预后评估能力、优缺点，其他新型功能学评价指标，以及功能指标临床预后评价的最新应用进展进行综述，从而指导临床在特定条件下使用特定的功能学评价指标或联合使用解剖学和功能学评价指标建立血运重建模式以减少假阳性和(或)假阴性，提高诊断的准确性。

［**关键词**］ 冠状动脉粥样硬化性心脏病；功能学评价指标；血流储备分数；瞬时无波形比值；定量血流分数；血运重建

［**中图分类号**］ R541.4　　［**文献标志码**］ A　　［**文章编号**］ 0577-7402(2021)11-1129-06

［**DOI**］ 10.11855/j.issn.0577-7402.2021.11.11

Progress on the application of coronary artery functional evaluation indices in percutaneous coronary intervention

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This work was supported by the National Natural Science Foundation of China (32071116), and the Project of Lixinyangfan Scientific and Research Fund (BJUHFCSOARF201901-14)

［**Abstract**］ The coronary artery functional evaluation indicators have been used recent years to evaluate the physiological function and judge the severity of coronary lesion, and provide the strategy of revascularization for patients with coronary atherosclerotic heart disease (CHD). As an invasive functional index, the efficiency of fractional flow reserve (FFR) has been widely testified by a large number of literature. However, due to its limitation in application, some FFR-based novel functional evaluation indices formed such as instantaneous wave-free reserve (iFR) and quantitative flow ratio (QFR). These indicators have their own characteristics, and provides some guidance and application value in revascularization for CHD patients although they haven't been widely used in clinical practice. The characteristics of coronary artery functional evaluation indicators, the assess capabilities of FFR, iFR and QFR to diagnosis and prognosis as well as strengths and weaknesses, the other novel functional evaluation indices, and the latest application progress of these functional indices in clinical prognosis evaluation have been reviewed in present paper, so as to guide the use of specific evaluation indicators under specific conditions, or combined use of anatomical and functional evaluation indicators to establish revascularization model to reduce false positive and/or false negative rates, so as to improve the accuracy of diagnosis.

［**Key words**］ coronary atherosclerotic heart disease; functional evaluation indices; fractional flow reserve; instantaneous wave-free reserve; quantitative flow reserve; revascularization

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［**基金项目**］ 国家自然科学基金(32071116)；“立信扬帆”优化抗栓科研基金(BJUHFCSOARF201901-14)

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冠状动脉粥样硬化性心脏病(coronary atherosclerotic heart disease，CHD)是一种严重威胁人类健康的心血管系统疾病。2019年全球疾病负担(global burden of disease，GBD)报告指出，缺血性心脏病是全球伤残调整寿命年(disability adjusted life year，DALY)增加的主要原因之一[1]。经皮冠状动脉介入术(percutaneous coronary intervention，PCI)是治疗CHD的有效方法，能够迅速恢复心肌血流灌注、减少心肌梗死面积，提高患者生存率及生存质量。对于梗死相关血管，一般依据冠脉造影结果行血运重建[PCI或者冠状动脉旁路移植术(coronary artery bypass grafting，CABG)]，而对于非梗死相关血管是否需要血运重建目前尚存在争议[2]，大多数患者行药物治疗，少部分依据冠脉造影结果行PCI治疗。由于患者的疾病预后与非梗死相关血管及临界病变的进展相关[3]，因此，合理的血运重建至关重要，而单纯依据冠脉造影结果进行指导具有一定的局限性。血流储备分数(fractional flow reserve，FFR)等冠状动脉功能学评价指标可为病变血管尤其是临界病变血管的血运重建提供一定依据[4-5]。因此，本文主要针对FFR、瞬时无波形比值(instantaneous wave-free reserve，iFR)、定量血流分数(quantitative flow ratio，QFR)及其他冠状动脉功能学评价指标在血运重建及预后评估中的价值进行综述。

1 概　　述

冠状动脉功能学评价指标是指用于判断冠脉病变是否导致心肌缺血，从而指导冠心病患者血运重建的功能性指标。这些指标不仅能够反映病变血管的形态学异常，还可用于评估病变血管功能改变的程度[3]。《冠状动脉血流储备分数临床应用专家共识》[4]及《中国经皮冠状动脉介入治疗指南(2016)》[6]均指出，FFR能够特异性反映冠脉狭窄的功能学严重程度，可用于评估临界病变、非罪犯血管及不明确的罪犯血管，此外，iFR等功能学指标目前仍在不断地进步发展。在指导血运重建方面，功能学指标与形态学指标有着相似甚至更好的结果，如一项Meta分析结果表明，FFR指导血运重建组的主要心血管不良事件(major adverse cardiovascular event，MACE)发生率明显低于冠脉造影(*OR*=1.71，95%CI 1.31~2.23)[7]。此外，与形态学指标相比，功能学指标指导下的血运重建的比例不高[8-11]，相关研究表明，这两种指标在指导中等病变程度血管的血运重建中存在约40%的不一致，主要与冠脉造影指导下的血运重建率更高有关[12]。总之，与冠脉造影相比，功能学指标能在达到相同预后结果的基础上降低血运重建率。

2 冠状动脉功能学评价指标的分类及优缺点

除FFR外，常见的功能学评价指标还包括iFR、冠状动脉血流储备(coronary flow reserve，CFR)、QFR等。FFR是指病变血管最大血流量与理论上该血管无病变情况下的最大血流量之比，可简化为在心肌最大充血状态下，狭窄远端冠状动脉内平均动脉压(Pd)与冠状动脉口部主动脉内的平均动脉压(Pa)之比[9]。CFR是指充血期和静息条件下冠状动脉血流速度之比或平均过渡时间之比[3,13]。iFR为FFR的改良版，是指静息条件下的舒张期Pd与Pa之比[14-17]。QFR为基于影像重建的FFR，是通过冠脉造影行3D重建计算的FFR值[18-20]。此外，还有其他类型的功能学评价指标，包括微循环阻力指数(index of microvascular resistance，IMR)、充血性微血管阻力指数(hyperemic microvascular resistance，HMR)[3]、基于光学相干断层扫描(OCT)测量的FFR值(optical coherence tomography derived-fractional flow ratio，OFR)[21]等。上述指标均有各自的优缺点，临床上应基于实际情况选择恰当的指标来指导血运重建，具体见表1。

3 各类冠状动脉功能学评价指标的临床应用价值

冠状动脉功能学评价指标可指导冠心病患者的血运重建，尤其对临界病变具有重要意义，能减少不必要的血运重建，提高其效率。目前，已有各具特色的多种功能学评价指标用于指导血运重建。

3.1 FFR的临床应用价值　欧洲心脏病学会(ESC)及欧洲心胸外科协会(EACTS)2019年联合发表的血运重建指南推荐FFR指导中等病变血运重建(Ⅰa)，并推荐FFR指导多支血管病变血运重建(ⅡaB)[22]。FFR诊断及预测预后的能力与冠脉造影无明显差异，甚至优于冠脉造影。DEFER研究发现，在冠脉造影结果相似的情况下，FFR<0.75的病变即使血运重建后，其预后也劣于FFR≥0.75的病变[23]。FAME研究发现，FFR指导的血运重建组1年死亡、非致死性心肌梗死及再次血运重建的复合终点发生率均低于冠脉造影组(13.2% *vs.* 18.3%，*P*=0.02)，2年的死亡及心肌梗死发生率低于冠脉造影组(8.4% *vs.* 12.9%，*P*=0.02)，但二者5年的终点结局事件发生率却无明显差异(28.0% *vs.* 31.0%，*P*=0.31)[24-26]。FAMOUS-NSTEMI研究[27]及COMPARE ACUTE研究[28]分别显示FFR在非ST段抬高型急性冠脉综合征(non-ST segment elevation acute coronary syndrome，NSTE-ACS)患者及ST段抬高型急性心肌梗死(ST segment elevation myocardial infarction，STEMI)患者

表1 各种冠状动脉功能学评价指标特点阐述

Tab.1 Characteristics of various coronary artery functional evaluation indices

功能学指标	公式	临界值	计算条件	优点	缺点
FFR	Pd/Pa	≤0.80	诱导充血期	提高冠脉造影对临界病变的诊断效能，现已成为评判冠状动脉缺血的金标准	操作时间长；花费高；患者不耐受
CFR	APVh/APVb Tmnb/Tmnh	<2.00	充血期和静息条件下	冠状动脉与微循环共同作用	无法区分冠状动脉与微循环血流受限；受静息条件下血流动力学的影响
IMR	Pd × Tmnh	>25.00 mmHg·s	诱导充血期	反映微循环功能；受血流动力学影响较小	–
HMR	Pd/APVh	>2.00 mmHg/(cm·s)	诱导充血期	反映微循环功能；受血流动力学影响较小	–
iFR	Pd/Pa	≤0.89	静息条件下舒张期	操作时间短；不需要诱导充血；与FFR有较好的一致性，可能成为替代FFR的指标	在特定人群中与FFR存在不一致性
Pd/Pa	Pd/Pa	<0.92	静息条件下整个心动周期	与FFR有较好的一致性	诊断效能劣于iFR；需连续分析数个波形；取值范围较窄
QFR	3D重建	≤0.80	3D重建	与FFR有较好的一致性；无需诱导充血；诊断效能不受患者对血管扩张剂反应性的影响	对造影影像质量要求高；术者操作对测量值的影响尚不明确；对特殊类型病变无法准确测量；对既往心肌梗死罪犯血管、微循环功能障碍的意义不明
OFR	OCT-FFR	≤0.80	无需诱导充血	相比于QFR及其他指标，与FFR有更好的一致性且不受既往心肌梗死及支架的影响	–

FFR. 血流储备分数；CFR. 冠状动脉血流储备；IMR. 微循环阻力指数；HMR. 充血性微血管阻力指数；iFR. 瞬时无波形比值；Pd. 狭窄远端冠状动脉内平均动脉压；Pa. 冠状动脉口部主动脉内平均动脉压；QFR. 定量血流分数；OFR. 基于光学相干断层扫描(OCT)测量的FFR值；APVh. 充血期峰速平均值；APVb. 静息峰速平均值；Tmnh. 充血期平均瞬时时间；Tmnb. 静息平均瞬时时间

中具有与冠脉造影相似的作用。同时，FFR在合并如重度贫血、败血症、心动过速、呼吸衰竭等疾病的患者中有一定的诊断价值，此类患者在冠脉造影或其他辅助条件下未检测到血栓形成、斑块破裂或其他形态学改变，却可能存在FFR阳性且与缺血相关的病变血管[29]。但FFR可能由于微循环功能障碍、冠状动脉钙化等原因引起充血期血流减少而增高，造成假阴性[30]，因此STEMI患者急性期(发病<6 d)FFR值可能会偏高，进而低估其病变程度[31]。

3.2 iFR的临床应用价值

3.2.1 iFR与FFR的相关性及诊断一致性 iFR为FFR的改良版，与FFR存在一定的线性关系(R^2=0.66)[17]，两者的区别主要是iFR的测量无需诱导充血[14-17]。iFR与FFR具有相似的诊断价值，且在二者指导下行血运重建后冠心病患者的MACE事件发生率接近，但iFR操作时间较短[32-34]。基于iFR与基于FFR行延期PCI的急性冠脉综合征(4.12% *vs.* 4.05%，*P*=0.60)[16,35]及前降支病变患者(2.44% *vs.* 5.26%，*P*=0.04)[36]的临床结果相似。iFR同样可用于指导有心肌梗死既往史的患者，iFR与FFR在指导治疗有无心肌梗死既往史的患者中均具有较好的一致性(*r*=0.81和*r*=0.72，*P*<0.001)，在联合使用iFR和FFR的策略下，二者的1年生存率接近(*HR*=0.87，95%CI 0.10~7.76，*P*=0.90)[15]。对于冠心病合并糖尿病患者，iFR组中非致死性心肌梗死发病率较高，但与FFR组比较差异无统计学意义(10.0% *vs.* 7.2%，*P*=0.30)[37]。总之，iFR具有与FFR相似的诊断和预测预后能力，且存在操作时间短、患者依存性好、支架置入较少及无需诱导充血等优势，有望取代FFR用于指导血运重建[16]。

3.2.2 iFR与FFR诊断的不一致性 在评价冠脉病变程度尤其是中等程度的病变时，约20%的病例FFR与iFR的结果一致[38-39]，可能与充血期血流速度[40]、基线血流量[39,41]及血管舒张功能[42]有关。高充血期血流速度可导致跨压差增大，进而使FFR减小，产生FFR(+)/iFR(–)的结果；基线血流量较少可使iFR增大，进而导致FFR(+)/iFR(–)；而微循环功能减退引起的血管舒张功能降低，可最终导致FFR(–)/iFR(+)[40]。导致FFR(+)/iFR(–)的因素包括年龄小、血栓位置(主要包括左主干和左前降支开口处病变)、病变程度重及心率慢，而导致FFR(–)/iFR(+)的因素包括年龄大、病变程度轻及不使用β受体阻滞剂[39]。此外，还有研究报道，性别、非透析状态、糖尿病、血栓形态可能均与FFR和iFR两个指标的诊断不一致相关[38-39,41]。在性别方面，男性易产生FFR(+)/iFR(–)的结果，而女性易产生FFR(–)/iFR(+)的结果，这可能与男性微循环功能较好、管腔面积较大、心脏舒张功能较差、心肌数量多或斑块性质等因素导致其在充血期血流较多，从而使FFR值变小有关，也可能与女性对充血反应较迟钝从而产生较大的FFR值[43-44]或静息状态下女性的血流较多从而产生较小的iFR值有关[41]。非透

析状态是FFR(+)/iFR(–)的独立影响因素，这与非透析患者基线血流量较少，进而导致iFR值较高有关[41]。还有研究发现，FFR(–)/iFR(+)的患者具有较高的糖尿病发生率，可能与糖尿病引起微循环功能障碍从而出现FFR(–)/iFR(+)有关[40]。此外，血栓自身形态对FFR与iFR的不一致性具有一定影响，以聚集为主的血栓容易导致FFR(+)/iFR(–)，而以弥散为主的血栓容易导致FFR(–)/iFR(+)[38]。尽管两项指标存在不一致的情况，但在预后方面，两者不一致且行延期PCI的患者5年后复合终点(patient-oriented composite outcome，POCO)发生率却无统计学差异[42]，因此，两者的不一致性对预后的影响不大，但需要依据不同的条件，选用合适的功能学指标来评价，以获得良好的效果。

3.3 QFR的临床应用价值 QFR是一项新型的功能学评价指标，是基于三维定量冠状动脉造影(three-dimensional quantitative coronary angiography，3D-QCA)计算FFR值的方法[18,45]。Smit等[46]发现，造影剂激发血流(contrast-flow QFR，cQFR)是负荷核素心肌灌注显像(SPECT-MPI)的独立影响因素，能较好地评估心肌缺血状态。FAVOR Ⅱ CHINA研究结果显示，以FFR为参考标准，QFR在患者水平与血管水平的术中评估诊断准确性分别为92.4%和92.7%，在血管水平的术后评估诊断性为93.3%，均明显高于定量冠状动脉造影(QCA)术中评估及术后分析的诊断准确性(分别为59.6%和64.0%)[47]。Hwang等[45]发现，在急性心肌梗死及稳定的缺血性心脏病中，QFR与FFR(r=0.863)或iFR(r=0.74)均有较好的相关性，且与FFR在评估非罪犯血管的病变程度上一致性较好[48]。此外，QFR还具有计算时间短[49]、无需使用导丝和血管扩张剂等优势[47]。因此，临床上QFR可用于对血管扩张药过敏以及无法进行FFR测量的患者，效果优于冠脉造影及FFR等金标准，并可用于线上指导血运重建。但在临界病变中，QFR与FFR同样存在约21.4%的不一致，且FFR(-)/QFR(+)往往与微循环功能差及血栓病变较重进而导致血流速度减慢有关[50]。PCI术后QFR对预后评估和预测有一定的帮助。Biscaglia等[20]发现，PCI术后QFR值是血管水平的复合终点事件(vessel oriented composite endpoint，VOCE)的独立影响因素，QFR≤0.89的血管较QFR>0.89的血管VOCE发生率高(25% *vs.* 3.5%，P<0.001)，提示QFR对支架置入后的预后预测能力较强。

4 冠状动脉功能学评价指标的应用进展

4.1 FFR测量方法学的改进 FFR的测量具有装置特殊、辐射较大及信号偏移等缺点，且由于需要使用血管扩张剂，FFR不能用于合并哮喘及重度房室传导阻滞的患者[29,51]。针对上述缺点，由FFR衍生出多种功能学评价指标，主要分为FFR的改良版及影像重建FFR，前者主要包括iFR、Pd/Pa、对比剂FFR(angiography-derived fractional flow reserve，FFRangio)，而后者主要包括QFR、OFR、冠状动脉CT血管成像FFR(computed tomography-fractional flow reserve，CT-FFR)。

4.1.1 FFRangio FFRangio是一种使用对比剂测量FFR值的无创性功能学评价指标，临界值以常规FFR为标准。相比于其他非充血期测量指标，FFRangio与常规FFR具有更高的一致性[52]，且较常规FFR有更高的诊断价值，但临床预后结果差异仍有待进一步验证[51,53]。

4.1.2 OFR OFR是基于OCT计算FFR值的方法，该方法可进行形态学及生理功能学评估[54]，且在罪犯血管、PCI术后血管、不同病变程度血管中进行测量时，与FFR均有较好的一致性，与QFR及传统形态学指标相比有一定优势，可更好地评估病变血管功能，进而提高PCI的使用效率[21,54-57]。

4.1.3 CT-FFR CT-FFR是一项基于CT计算FFR值的方法，与常规FFR测量有较好的一致性[58]。在短期随访中，该指标与常规指标在终点事件发生率上相似，同时还具有诊断价值较好、花费少、生存质量较高等优点，但该值受CT分辨率的影响[51]，此外还缺乏长期随访的证据[59]。

4.1.4 FFR测量方法的改进 微导管FFR值测量技术(microcatheter derived FFR，mc-FFR)具有导丝位置稳定，可在较少的信号漂移下重复测量等优势。但mc-FFR与常规FFR比较有一定的差异，主要与OCT测量下的最小管腔面积(r=–0.3359)、病变长度(r=0.07)及mc-FFR值(r=–0.603)相关[60]。

4.2 联合指导血运重建 由于iFR与FFR存在不一致性，以FFR≤0.80为参考标准，iFR的诊断准确性为84%，但iFR与FFR联合指导血运重建则可使诊断准确性达到90%，且约64.9%的病变血管可避免使用腺苷诱导充血[17]。因此，为降低操作难度及减少不良反应，可联合应用FFR与iFR指导血运重建，即当iFR值在0.86~0.93时计算FFR值，当iFR<0.86时进行血运重建，而当iFR>0.93时则延期进行血运重建。该指导方式与FFR的不一致率约为9.4%，低于单独使用iFR与FFR的不一致率[61]。因此，联合指导血运重建可在提高准确性的同时，减少FFR测量的不良反应。

4.3 预后评分系统 基于QFR测量的评分系统有两种，一种是计算3支血管的QFR之和(three-vessel contrast-flow quantitative flow ratio，3vQFR)

来预测患者的预后，3vQFR值是MACE的独立影响因素(*HR*=0.971)[18,62]；另一种是基于QFR的功能性SYNTAX评分(functional SYNTAX score derived from QFR，fSSQFR)，即计算QFR≤0.8的病变血管SYNTAX评分，当fSSQFR>0时心血管事件发生率较高，且其预测预后的能力也高于传统SYNTAX评分(classic anatomic SYNTAX score，cSS)[18,63]。此外，在血运重建后，采用基于QFR的SYNTAX评分(quantitative flow ratio guided residual functional SYNTAX score，Q-rFSS)进行分组，不完全血运重建组MACE事件发生率较完全血运重建组高(22.0% *vs.* 7.4%，*HR*=3.21，*P*≤0.001)，且缺血驱动的血运重建发生率也高(19.3% *vs.* 4.4%，*HR*=4.74，*P*<0.001)，提示采用Q-rFSS进行危险等级评估较残余SYNTAX评分(residual SYNTAX score，rSS)评价效果好，QFR可作为提高SYNTAX评分预后预测能力的补充指标[64]。

5 总结与展望

FFR、iFR和QFR作为评价病变程度的功能学指标，不仅可指导血运重建，还可用于评估PCI术后患者的预后[20,37]。冠状动脉的病变程度尤其是临界病变不能单纯依靠冠脉造影结果来评判，还需借助冠脉腔内影像及功能学指标进行综合判断，从而最终确定是否需要进行血运重建。此外，针对单支多处血栓病变，采用常规的针对单个血栓的评价方式达不到评价血栓病变程度的效果，因此需要结合功能学及形态学特点对单个血栓的病变程度进行综合诊断，根据临床症状、冠脉腔内影像、功能学评价，以及有无病变分支等特点决定是否需要行血运重建[65]。

综上所述，FFR目前已成为评价冠脉病变严重程度的金标准，可为临界病变提供一定的诊断作用，但因存在一定局限性，在临床上的应用并不广泛。因此，FFR的改良版和影像重建FFR逐渐发展起来。iFR作为FFR的改良版，因具有测量时间短、无需使用血管扩张剂的特点，可用于无法测量FFR的患者，但仍为有创性指标。QFR则是一种无创的影像重建FFR，且与FFR一致性较好，具有较好的诊断及预后评估能力。此外，OFR作为另一种影像重建FFR，可在功能学评估的同时评价支架的放置情况，因此有望为将来指导血运重建尤其是临界病变提供更好的客观证据。各类指标均存在相应的诊断、预后评估能力及优劣势，在以后的研究中可针对各类功能学指标的缺点进一步改进，或联合使用多种功能学和形态学指标，进而合理地进行诊断并指导血运重建，以获得较好的诊断及预后结果。

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(收稿日期：2021-01-25；修回日期：2021-06-16)
(责任编辑：张小利)