

· 主题综述 ·

核素心肌血流定量新技术的研究和临床应用进展

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【摘要】近年来,随着冠心病诊疗水平的提高,对冠状动脉功能学诊断技术的需求日益增长。放射性核素心肌灌注显像正逐步从视觉定性诊断向更为精准的定量诊断转变,心肌血流定量技术日益完善,初步的临床研究已显示出很好的应用前景。现综述核素心肌血流定量技术的特点、发展现状和临床优势,为这一新技术的普及应用和更多的临床研究提供参考和借鉴。

【关键词】冠心病;心肌灌注显像;心肌血流量;心肌血流储备

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Research and Clinical Application of New Technique for Radionuclide Myocardial Blood Flow Quantification

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【Abstract】With the development of diagnosis and treatment of coronary heart disease in recent years, there is an increasing demand for coronary functional diagnostic technique. Radionuclide myocardial perfusion imaging is transforming from qualitatively visual diagnosis to quantitatively precise diagnosis. Quantification of myocardial blood flow technique has been improved and shown promising prospects in preliminary clinical studies. This article will review the technical considerations, current development and clinical advantages of radionuclide myocardial blood flow quantification, offering evidence and reference for the wide application and further research of this new technique.

【Key words】Coronary heart disease; Myocardial perfusion imaging; Myocardial blood flow; Myocardial flow reserve

放射性核素心肌灌注显像(myocardial perfusion imaging, MPI)是一种常用的冠心病心肌缺血诊断、危险分层和治疗决策的无创性影像学技术^[1],根据使用的放射性显像剂和显像仪器的不同,分为单光子发射计算机断层成像(single photon emission computed tomography, SPECT)和正电子发射断层成像(positron emission tomography, PET)两种方法。PET较SPECT有更高的探测灵敏度和空间分辨率,但成本较高,价格昂贵,因此临床应用受到一定限制。SPECT MPI应用更为普及,显像剂主要有^{99m}Tc-MIBI、^{99m}Tc-tetrofosmin和²⁰¹Tl等;而PET MPI的显像剂有¹³N-NH₃、⁸²Rb和¹⁵O-H₂O等,其中¹³N-NH₃和⁸²Rb较为常用。上述心肌灌注显像剂在心肌细胞的摄取和分布与心肌血流量(myocardial blood flow, MBF)呈正相关,因此可用来评价心肌供血情况。以往MPI主要依靠视觉分析,根据心肌断层图像中是否存在放射性摄取减低而判断是否存在心肌缺血改变。近年来,基于

MPI的心肌血流绝对定量技术逐步成熟,能提供负荷状态和静息状态下的MBF和冠状动脉血流储备(coronary flow reserve, CFR)或心肌血流储备(myocardial flow reserve, MFR)等定量指标,并已开始应用于临床,现对核素心肌血流定量技术的意义、技术发展及临床应用进行综述。

1 心肌血流定量的重要意义

以往冠状动脉造影一直被认为是诊断冠心病的“金标准”,但实际上冠状动脉造影只能提供冠状动脉狭窄的解剖学信息,而冠状动脉的狭窄严重程度与血流动力学的功能变化并不完全对应^[2],许多患者虽然存在着一定程度的冠状动脉狭窄,但并不意味着一定存在着血流动力学的异常,即不一定存在功能性的心肌缺血。2007年发表的COURAGE试验^[3]结果表明,冠状动脉狭窄程度≥70%的慢性稳定性冠心病患者,接受血运重建与单纯药物治疗相比,预后并未显著获益。其后的FAME系列研究^[4,5]采用了有创压力导丝

测定的血流储备分数(fractional flow reserve, FFR)指导血运重建治疗,最终使患者的临床结局得到显著改善,表明冠状动脉血流的功能学指标作为血运重建治疗决策的依据更为合理。目前国际指南^[6]已明确推荐在血运重建治疗前需测定 FFR 以获得心肌缺血的证据。但由于 FFR 是有创检查,成本也较高,目前在国内外开展得并不普遍。另一方面,FFR 仅能反映冠状动脉大血管的功能变化,而同时反映冠状动脉微血管病变则需测定 CFR 或 MFR。目前,测定 CFR 或 MFR 可依靠无创性影像学技术,包括 PET 或 SPECT 心肌血流定量技术和心脏磁共振心肌灌注成像技术,前者更为成熟,其中 PET 目前被认为是定量心肌血流的“金标准”,而 SPECT 由于成本更低,易于普及,近年来发展很快,特别是图像重建和物理校正技术的显著提高,使 SPECT 心肌血流定量技术已逐步完善,并开始应用于临床。

2 核素心肌血流定量技术的发展

2.1 PET 心肌血流定量技术

与常规 PET MPI 的静态采集方式不同,心肌血流定量需采用动态采集技术,即在显像剂注射的即刻就启动连续采集模式,观察心肌对显像剂的“首次通过提取”,并完整记录显像剂从动脉血分布至心肌的全过程。图像重建和校正后,将左心室血池的时间活度曲线作为输入函数,以适当的动力学模型对心肌的时间活度曲线进行拟合,获得显像剂进入心肌细胞的速率 K_1 ,并经由已知的显像剂心肌提取率对 K_1 进行转换,从而获得心肌的绝对血流量 MBF,包括血管扩张药物负荷状态下测定的 MBF 和静息状态下的 MBF,负荷与静息的 MBF 之比即为 MFR(或 CFR)。

PET 心肌血流定量的准确度取决于几个因素,包括左心室的分割勾画、输入函数感兴趣区的定位、探测器的灵敏度以及算法的使用等^[7]。研究^[8]表明,目前使用的基于不同分割算法的后处理软件彼此间具有良好的相关性。由于目前 PET/CT 的一体化,CT 可辅助进行衰减校正。由于 PET 具有较高的探测灵敏度、时间分辨率和空间分辨率,因此进行心肌血流定量具有较好的优势。

已有研究证实 PET 心肌血流定量具有较好的准确度,荷兰阿姆斯特丹自由大学医学中心的 PACIFIC 研究^[9]中,以 $FFR \leq 0.8$ 或冠状动脉狭窄 $\geq 90\%$ 作为功能性缺血的“金标准”, $^{15}\text{O-H}_2\text{O}$ PET 心肌血流定量以负荷 $MBF \leq 2.30 \text{ mL}/(\text{min} \cdot \text{g})$ 为界值,诊断心肌缺血的灵敏度和特异度在患者水平分别为 87% 和 84%,在血管水平分别为 81% 和 75%。PET 心肌血流定量的诊断准确度明显高于 CT 冠状动脉造影和常规

SPECT MPI。随后的 PACIFIC 2 研究^[10]以同样的方法,发现对于既往有心肌梗死或血运重建病史的患者, $^{15}\text{O-H}_2\text{O}$ PET 心肌血流定量诊断心肌缺血的准确度明显优于心脏磁共振 MPI 和 SPECT MPI。另一项研究^[11]发现, $^{13}\text{N-NH}_3$ PET 心肌血流定量指标与 FFR 有很好的相关性,其中负荷 MBF 的相关性较 MFR 更好。

2.2 SPECT 心肌血流定量技术

PET 心肌血流定量虽然更为准确,但由于显像剂标记使用的放射性核素均为超短半衰期核素,如 ^{13}N 、 ^{82}Rb 和 ^{15}O 的物理半衰期分别为 10 min、76 s 和 2 min,不可能远程商业配送,必须配备现场回旋加速器或核素发生器,成本昂贵,不利于临床推广应用。如果成本较低的 SPECT 能实现心肌血流定量,将是更为理想的选择。

与 PET 相比,SPECT 心肌血流定量的技术难度更大。首先,要实现动态断层采集。PET 探头是环状设计,比较容易实现;而 SPECT 多是单探头或双探头设计,实时动态断层采集比较困难。其次,SPECT 要进行更为复杂的物理校正,包括移动校正、散射校正、组织衰减校正和图像空间分辨率恢复等;配置针孔准直器的 SPECT 还需增加几何扭曲校正和数据截断补偿。再次,SPECT 探测灵敏度和信息量相对较低,图像噪声较高,需新的重建算法有效降低噪声,提高定量的准确度。

碲锌镉(cadmium zinc telluride, CZT)固态半导体探测器是近年来 SPECT 探测技术的重大进展,CZT SPECT 探头呈半环或全环设计,能实现实时动态采集,CZT 材料的探测灵敏度是传统 NaI 探测器的 7 ~ 8 倍^[12]。因此,CZT SPECT 非常适用于心肌血流定量的要求。临床应用研究^[13]表明,CZT 测定的 MBF 与 $^{13}\text{N-NH}_3$ PET 有很好的相关性。WATERDAY 研究^[14]也发现,与 $^{15}\text{O-H}_2\text{O}$ PET 相比,CZT SPECT 在不进行衰减校正的情况下,尽管负荷和静息 MBF 有所高估,但 MFR 无显著差异。针对 SPECT 噪声比较高的特点,还有研究^[15]在传统的有序子集最大期望值法重建方法基础上,增加样条拟合重建技术,能有效地降低噪声,显著改善了 SPECT 与 PET 的血流定量指标的相关性和一致性,检测的可重复性也明显提高。

尽管如此,CZT SPECT 相对于传统 NaI SPECT 仍较为昂贵,因此能否采用更普及的 NaI SPECT 进行心肌血流定量成为新的挑战。有研究利用 NaI SPECT 探头的快速旋转功能,并对不一致的投影角度信息进行校正和补偿,从而实现了动态断层采集。在进行充分的物理校正的基础上,NaI SPECT 测定的 MBF 和 MFR

可与 CZT SPECT 和 PET 十分接近^[16-17], 初步的临床研究也显示出较好的诊断效能^[18]。

3 核素心肌血流定量技术的临床应用

3.1 提高心肌缺血的诊断效能

传统的 MPI 仅能对图像进行视觉或半定量分析, 通过比较心肌各节段放射性分布的相对差异来鉴别缺血区域。当冠状动脉左主干或多支病变以及冠状动脉弥漫性病变造成心肌血流普遍减低, 形成“均衡缺血”时, 视觉判读 MPI 可能会误判为正常, 或低估病变的程度及范围, 形成假阴性诊断^[19]。而心肌血流定量技术则能有效地解决这一问题, 提高诊断的灵敏度。

已有的研究^[20]认为, 在⁸²Rb PET 心肌血流定量分析中, 患者整体心肌的 MFR < 2.0 时被认为是冠状动脉三支病变的独立预测因子。另一项研究^[21]发现, ¹³N-NH₃ PET MPI 结合 MFR < 2.0 作为心肌缺血的判定标准, 将诊断的灵敏度从 79% 提高到 96%, 准确度从 79% 提高到 92%, 具有显著的增益作用。而 SPECT 心肌血流定量研究^[22-23]也认为, 负荷 MBF 和 MFR 等定量指标的诊断准确度明显优于常规 SPECT MPI。

3.2 在冠心病危险分层及预后评价中的应用

Herzog 等^[24]的研究发现, 尽管 PET MPI 视觉评估未见异常, 但如果发现 MFR 异常, 则患者发生心血管不良事件的概率显著增高。以后又有多个研究进一步证实 MFR > 2.0 的患者发生心血管不良事件的概率要明显低于 MFR 受损的患者^[25]。除此之外, 还有研究^[26]认为, MFR 有助于优化冠心病的风险分层, 可将 51% 的冠心病中等风险人群重新分类, 其作用超过了临床综合风险评估、左室射血分数、心肌缺血或梗死的程度及范围等指标。

3.3 在冠状动脉微血管功能障碍中的应用

冠状动脉微血管功能障碍 (coronary microvascular dysfunction, CMD) 在具有心血管危险因素的患者中普遍存在, 并且与心血管不良事件的风险显著相关。CMD 有效治疗的前提是准确的诊断和能对疗效进行评价^[27]。现有的诊断技术难以直观地显示冠状动脉微血管的解剖结构, 但可评估其功能状态。目前的冠心病诊疗指南^[28]推荐 PET 和心脏磁共振等用于 CMD 的诊断。有研究^[29]表明, 当心外膜冠状动脉未见明显狭窄时, PET 测定的 MBF 和 MFR 等指标的减低可提示存在 CMD。

除了辅助诊断 CMD, PET 血流定量更重要的意义在于评估 CMD 患者的预后, 这方面的证据也最为充分。对于心肌病患者, 有研究表明负荷 MBF 是肥厚型

心肌病^[30]和特发性心肌病患者^[31]发生不良预后的有效预测因子, 而 MFR 受损的缺血性心肌病患者发生心源性死亡的风险更高^[32]。

PET 心肌血流定量技术在一些特殊风险人群中也有应用, 如糖尿病、慢性肾脏病和心血管代谢疾病等患者, 即使冠状动脉造影阴性, 其 MFR 往往低于正常人^[33]。性别对于 CMD 的影响也值得重视, 女性更容易表现为心绞痛症状明显但冠状动脉造影结果正常, 提示女性发生 CMD 的概率更高^[34]。对于上述这类特殊风险人群, MFR 受损同样提示患者预后不良^[35]。

3.4 在心脏移植术后心脏移植血管疾病中的应用

心脏移植血管病变 (cardiac allograft vasculopathy, CAV) 是同种异体心脏移植术后患者发生心源性死亡的重要原因^[36]。移植过程中心脏失去神经支配, CAV 通常以无症状形式进展, 因此早期检测对于 CAV 的及时治疗至关重要。目前, CAV 的首选诊断方式是冠状动脉造影。但 CAV 以心外膜大血管及微循环的内膜弥漫和向心性增厚为特征, 这与冠状动脉疾病中常见的局灶和偏心性分布的斑块形成对比^[37], 造影的诊断价值受限。越来越多的证据^[38]支持 PET 心肌血流定量在 CAV 的诊断及预后价值评估中均有重要作用。

Bravo 等^[39]发现用¹³N-ammonia PET 心肌血流定量获得的负荷 MBF 有助于区分中重度与轻度的 CAV 患者。Chih 等^[40]用侵入性血管内超声作为诊断标准的研究进一步表明无创性⁸²Rb PET 心肌血流定量获得的 MBF 和 MFR 与侵入性检查测得的冠状动脉血流量和 CFR 显著相关。除了诊断价值, PET 心肌血流定量对 CAV 的风险分层及预后评估也有重要作用。几项研究^[41-43]均证实 MFR 是心脏移植术后患者发生心血管不良事件的有力预测因子。Feher 等^[44]研究进一步表明, 在中位随访时间为 8.6 年的 89 例心脏移植术后患者中, MFR 在经过多因素模型的校正后仍可独立地预测心脏移植术后患者的长期死亡率。

4 总结和展望

综上所述, 核素心肌血流定量技术使 MPI 从传统的定性诊断向更为精准的定量诊断转变, 显著提高了冠状动脉多支病变和弥漫性病变心肌缺血的诊断准确度, 对于冠状动脉微血管病变的诊断也具有独特的价值。虽然 PET 成本较高, 但随着 SPECT 心肌血流定量技术的逐步完善, 临床应用会更加广泛, 作为重要的冠状动脉功能学诊断技术, 在冠心病的诊断、危险分层、治疗决策和疗效评估等方面必然发挥更重要的作用。目前, 核素心肌血流定量的临床研究还相对较少, 未来还需开展更多经过严格设计的多中心及前瞻

性研究,为这一技术的合理应用提供更加充分的研究证据。

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