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MRI对乳腺癌药物治疗所致心脏毒性的早期检测

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摘　要

有数据显示，乳腺癌已占据女性癌症发病率和死亡率的首位，但得益于医疗水平的进步，患者的生存时间整体延长。然而代价是心脏毒性和心功能不全的风险增加，有必要引起医生足够的警惕和重视。心脏磁共振(Cardiac Magnetic Resonance, CMR)可显示心脏的结构、功能及心肌组织特征，其先进的测量应变及mapping技术可早期发现心肌损伤，包括心肌水肿、纤维化及亚临床心肌功能改变等。总之心脏MRI可早期发现乳腺癌治疗所致心脏毒性，并对后续的监测、疗效评估及预后判断具有重要的临床价值。本文就MRI对乳腺癌药物治疗所致心脏毒性的早期检测作一综述。

关键词

磁共振成像，乳腺癌，心脏毒性，化学治疗，靶向治疗

Early Detection of MRI Cardiac Toxicity Caused by the Treatment of Breast Cancer Drugs

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Abstract

Some data show that breast cancer has occupied the first place in terms of cancer morbidity and mortality in women, but due to medical advances, patients have an overall longer survival time. The cost, however, is an increased risk of cardiotoxicity and cardiac insufficiency, warranting sufficient vigilance and attention from physicians. Cardiac Magnetic Resonance (CMR) reveals the structure, function, and myocardial tissue characteristics of the heart, and its advanced strain and mapping techniques allow for early detection of myocardial injury, including myocardial edema, fibrosis, and subclinical myocardial functional changes. In conclusion, cardiac MRI can provide early detection of cardiotoxicity due to breast cancer treatment and is clinically important for follow-up monitoring, efficacy assessment, and prognosis. In this paper, we review the early detection of cardiotoxicity due to breast cancer drug therapy by MRI.

Keywords

Magnetic Resonance Imaging, Breast Cancer, Cardiotoxicity, Chemotherapy, Targeted Therapy

1. 引言

目前，乳腺癌占全球女性癌症发病率和死亡率的首位，且在中国的发病率还在快速升高[1]，但得益于医疗水平的进步，患者生存时间明显延长[2]。然而，癌症治疗产生的心脏毒性对幸存者生存质量的影响越来越大，早期发现及监测心脏毒性是必不可少的[3] [4]。心脏磁共振(Cardiac Magnetic Resonance, CMR)具有多参数，多序列，可重复，无创等优点，其先进的应变及 mapping 等技术可在左室射血分数(Left Ventricular Ejection Fraction, LVEF)下降之前早期发现心肌损伤，为临床早期干预提供重要信息。

2. 常用药物及致病机制

乳腺癌治疗常用传统化疗药包括：① 蒽环类，如阿霉素、柔红霉素等；② 烷化剂，如环磷酰胺、铂类等；③ 抗代谢药，如 5-氟尿嘧啶、甲氨蝶呤和卡倍他滨等；④ 微管抑制剂，如紫杉醇、多西他赛等。乳腺癌治疗常用靶向药物为 HER2 受体抑制剂，如曲妥珠单抗、帕妥珠单抗、奈拉替尼等。

2.1. 传统化疗药

蒽环类药物是乳腺癌化疗最常用的药物，但其所致心脏毒性的风险也是最大的。蒽环类药物对心脏的损伤主要是通过抑制心肌拓扑异构酶 IIβ，影响 DNA 的转录和复制[5]，进而导致过量活性氧(Reactive Oxygen Species, ROS)产生和线粒体损伤[6]，最终可致心肌细胞纤维化、萎缩、凋亡甚至坏死[7] [8]。蒽环类药物相关心力衰竭(Heart Failure, HF)是剂量依赖性的，一项回顾性研究表明，大多数事件发生在累积剂量 $\geq 500\ mg/m^2$。总体而言，累积剂量为 400 mg/m^2 时，HF 的发生率约为 5%，500 mg/m^2 时为 16%，550 mg/m^2 时为 26%，700 mg/m^2 时为 48% [9]。然而，患者对蒽环类药物的敏感性存在很大的差异。虽然许多人耐受标准剂量的蒽环类药物，没有长期并发症，但其他患者可能最早在第一次服药后就出现与治疗相关的心脏毒性[10]。

环磷酰胺的心脏毒性相对罕见，主要见于给予较高单剂量药物治疗的患者。心力衰竭通常发生在给药后 3 周内，降低该药物的剂量可大大降低这些不良事件的发生率[11]。含铂的化疗需要高静脉输液量，以避免铂相关的毒性。但是已经存在心肌损伤的患者的这种容量超负荷，往往是导致首次或反复发作心力衰竭的原因，而不是这些药物的直接毒性[12]。

5-氟尿嘧啶(5-FU)及其口服前体药物卡培他滨可导致心肌缺血，发生率通常 < 10% [13]。缺血的机制可能与其诱导冠状动脉痉挛有关，潜在的冠状动脉疾病似乎增加了这种风险。与 5-FU 相关的心脏毒性似乎主要与其给药程序有关，而不是与使用的剂量有关。持续输注比推注有更高的风险[14]。

紫杉醇导致心律失常的原因可能是细胞器的损伤[14]。多烯紫杉醇与蒽环类药物、环磷酰胺或曲妥珠单抗联合使用或后续使用，是否会增加心力衰竭的发病率还未确定；因为，在多药联用方案中单独使用药物的作用往往很难评估[12]。

2.2. HER2 受体抑制剂

曲妥珠单抗可抑制心肌细胞人表皮生长因子受体，从而导致线粒体和收缩蛋白的 ATP 耗竭和收缩功能障碍。与 HER2 阳性乳腺癌患者心脏毒性相关的主要药物包括蒽环类药物和曲妥珠单抗[15]。在 HER2 阳性的乳腺癌患者中，由于癌症治疗而导致的主要心脏事件的 5 年累积发生率估计为 4.13%，而在普通非癌症人群中相应的发生率为 1.68% [16] [17]。当蒽环类药物与曲妥珠单抗联合使用时，患者的无病生存期和总生存期显著增加，但心脏毒性发生率很高。已知曲妥珠单抗导致心脏毒性的病理生理机制与直接对心肌细胞造成结构性损害的蒽环类药物相反，其作用机制包括通过抑制信号转导、新血管生成和修复其他治疗方法造成的 DNA 损伤而产生细胞毒性[18]。这些损害机制可能解释了同时使用曲妥珠单抗和蒽环类药物会增加心脏毒性的风险。曲妥珠单抗可以通过干扰细胞生存和修复的稳态机制和途径来加重和加速先前的蒽环类药物治疗造成的损害[19]。

3. 心脏磁共振研究进展

3.1. 心脏结构序列

常规轴位、冠状位和矢状位的 T1 和 T2 加权定位图像提供了有关心胸结构的基本形态数据[20]。尤其是乳腺癌患者，可表现为药物相关的 HF 所致的胸腔积液。此外，可以确定转移灶，这可能有助于设计治疗策略。

3.2. 心脏功能序列

常规电影序列可提供射血分数、每搏输出量、容积、心肌质量及心指数等多种功能信息，并且具有良好的可重复性及较高的观察者间和观察者内的一致性[21]。CMR 是目前检测和监测心室功能和容量的金标准[22]。

癌症治疗可导致 LVEF 下降，由于心脏本身的代偿机制，当 LVEF 出现明显下降时，往往已经发生了不可逆的损伤[23]。组织学研究表明，在接受心脏毒性化疗后，左心室射血分数下降之前，心肌细胞受损就是佐证[24]。因此，以 LVEF 评价心脏毒性较为滞后，不能及时发现亚临床心功能损伤，而使患者错失最佳治疗时间窗。

特征追踪(Feature Tracking, FT)技术可以利用电影序列计算心肌应变。尽管 LVEF 正常，但在乳腺癌患者中可发现 FT 计算的整体纵向应变(Global Longitudinal Strain, GLS)和整体周向应变(Global Circle Strain, GCS)异常，并且 GCS 的下降已被证明可以预测 LVEF 在接触蒽环类药物 3 个月后的下降[25]。在一组接受蒽环类药物治疗且 LVEF 正常的血液癌症患者中，基线整体纵向应变 < −17.5%的患者心源性死

亡或有症状的心力衰竭的概率增加 6 倍[26]。另一种测量应变的方法是通过 Fast-SENC 获得，这种方法快速且不依赖于屏气动作。Sorin Giusca 等人基于 Fast-SENC CMR 提出的正常心肌百分比(%)，可以确定接受化疗的癌症患者的心脏安全性，不仅可以早期发现，还可以预测那些有发展成亚临床心脏毒性风险的人[27]。

左心室舒张末期容量(Left Ventricular End-diastolic Volume, LVEDV)和左心室收缩末期容量(Left Ventricular End-systolic Volume, LVESV)的变化在 LVEF 出现任何可察觉的下降之前就出现了，并且可以通过电影序列很好地显示出来[28]。而且服用蒽环类药物后左心室质量减少，其可能是心肌细胞萎缩所致[8]。左心室质量是一个重要的心血管事件预测因子，当左心室质量 < 57 g/m^{2}时，发生心血管死亡事件的风险明显升高[29]。

CMR 的空间分辨率足以表征右心室(Right Ventricle, RV)心肌，提供对 RV 功能的准确评估。曲妥珠单抗已被证明可引起右心室射血分数(Right ventricular ejection fraction, RVEF)的轻微下降，似乎在治疗完成 6 个月后开始恢复，18 个月后恢复正常[30]。这种现象在蒽环类药物中也有报道[31]。而且有研究发现 LVEF 和 RVEF 的时间变化模式可能是平行的，尽管只发现了不显著的相关性[30]。

由于 CMR 监测 RV 心肌应变的数据很少，其长期预测意义在很大程度上是未知的。有关心脏超声的研究发现，在接受表柔比星治疗的乳腺癌患者中，右室游离壁纵向应变(Free Wall Longitudinal Strain, FWLS)的下降与呼吸困难的发展显著相关，与左、右室收缩和舒张期功能无关[32]。此外，在同时接受化疗和放疗的 III 期非小细胞肺癌患者中，RV FWLS 的基线和百分比变化已被证明是全因死亡率的独立预测因素[33]。有研究发现 RV 容量的显著增加也可以指示心脏毒性[30]。

CMR 可准确测量左心房(Left Atrium, LA)的大小，研究显示暴露于蒽环类药物的患者 LA 大小增加[34]。同时 CMR 卓越的空间分辨率提供了 LA 心肌特征追踪的额外好处，以确定整个左心房排空周期中的 LA 应变[35]。

3.3. 心肌组织特征序列

CMR T1 mapping 和 T2 mapping 技术是一种很有前途的非侵入性工具，可通过纵向和横向弛豫的变化量化心肌组织变化，从而早期识别心脏毒性[36]。延迟钆剂强化(Late Gadolinium Enhancement)难以检测到弥漫性纤维化，但 Native T1 能够在不使用钆剂的情况下检测局部或弥漫性心肌病变过程引起的心肌变化[37]，通过增强后 T1 mapping 可量化细胞外体积(Extracellular Volume, ECV)，精确评估心肌组织变化。ECV 增加可能是由扩大细胞外空间的因素(例如弥漫性纤维化和/或水肿)或减少心肌体积的因素(例如心肌细胞大小和/或数量减少)引起的。细胞内水寿命(intracellular water lifetime, τic)和 T2 值有助于确定哪个过程导致间质空间增加：是由于水肿(T2 增加)、心肌细胞萎缩(τic 降低)还是间质纤维化(T2 正常或降低，τic 正常或升高) [8] [38]。接受蒽环类药物 48 小时后 Native T1 值的急剧下降预示着随后可能发生心肌病[37]，2 个月后 Native T1 的升高可预测 18 个月后 LVEF 的下降[39]。有动物实验结果表示，LV 心肌的 ECV 值在左心室射血分数下降前 3 周显著升高，且 RV 上下附着点和乳头肌的 ECV 均超过 LV；LV 中段 Native T1 值从第 6 周开始显著增加，心肌 ECV 与纤维化程度呈正相关[40]。

T2 mapping 已被证明是一种高度可重复性的量化细胞内和/或细胞外心肌水肿的技术。T2 延长(T1 和 ECV 正常)反映了心肌细胞内的细胞水肿，并代表了可逆性蒽环类药物心脏毒性的早期成像标志物。T2 延长后继续使用多柔比星导致 LVEF 明显下降，同时伴有 Native T1 延长、ECV 增加和与蒽环类药物心脏毒性特征一致的组织学变化(即心肌细胞内空泡化、细胞外空间增加和纤维化)。在检测到 T2 延长后停用蒽环类药物可防止蒽环类药物心脏毒性的临床和病理变化的发展[41]。同时 T2 mapping 信号升高和延迟增强为心肌炎症的存在提供了强有力的支持性发现，而心包强化和 LVEF 降低被认为是支持性发现。

关于 LGE 的显示及预后作用观点不一。有研究发现 LGE 仅存在于少数群体中。它的模式和位置不适合单个独特的特征。它几乎在所有情况下都有替代解释。最后，LGE 也存在于既没有接受蒽环类药物也没有接受曲妥珠单抗治疗的癌症患者中。因此，蒽环类药物和/或曲妥珠单抗治疗不太可能与 LGE 相关[42]。但有动物实验发现在注射 DOX 后，钆信号的低测量值预示着没有 LVEF 下降或意外死亡。DOX 后钆信号的增加预示着随后的 LVEF 下降，以及与 DOX 心脏毒性相一致的细胞内空泡化的组织病理学证据[43]。

3.4. 血管评估序列

化疗导致的血管毒性机制多种多样，通常涉及过量的 ROS，导致促炎细胞因子的释放和细胞信号转导中断，导致心外膜和微血管冠状动脉床的内皮损伤和血管收缩[44]。负荷 CMR 已被证明是诊断和对疑似或已知的心外膜冠心病患者进行风险分层的有效手段[45] [46] [47]，且可量化心肌血流(Myocardial Blood Flow, MBF) [48]。有初步研究发现，暴露于潜在心脏毒性化疗的乳腺癌患者中，基于 CMR 的定量灌注指数与 LVEF 相关，这意味着微血管功能障碍可能与癌症治疗相关的心功能不全(Cancer Therapy Related Cardiac Dysfunction, CTRCD)相关[49]，并且可能在 LV 明显降低之前检测到功能障碍。另外，负荷 T1 mapping 已被证明与钆剂首过灌注一样准确，并且可以在不使用造影剂的情况下可用于评估先前暴露于蒽环类药物的患者的微血管功能障碍，可作为钆剂首过灌注的合理替代方案[50]。

主动脉脉搏波速度(Pulse Wave Velocity, PWV)已被用于测量主动脉扩张性，与 LV 后负荷增加、LV 功能降低和非肿瘤患者死亡率增加相关[51]。主动脉 PWV 在暴露于蒽环类药物[52] [53]和曲妥珠单抗后早期增加，在停止治疗后似乎部分消退[54]。主动脉僵硬的机制尚不清楚，但随着时间的推移，僵硬的消退意味着内皮功能障碍，而不是随着年龄或高血压出现的典型的纤维化僵硬机制[52]。需要进一步的研究来确定这些发现的长期意义。

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