

多模态超声评估乳腺癌双靶向治疗后右室功能

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摘 要

人类表皮生长因子受体2 (Human epidermal growth factor receptor 2, HER2)阳性乳腺癌侵袭性强, 以曲妥珠单抗、帕妥珠单抗为核心的TCbHP方案(紫杉类 + 卡铂 + 曲妥珠单抗 + 帕妥珠单抗)显著改善了患者预后, 但治疗相关心脏毒性成为影响长期生存的重要问题。既往监测多聚焦于左心室射血分数, 对右心室关注不足, 而右心室损伤往往隐匿且可能早于左心室出现。本文阐述靶向药物及化疗的协同心脏毒性机制, 重点评述单一技术(常规超声、斑点追踪成像、四维右室容积定量)及四维右室容积定量联合斑点追踪成像技术在右心室功能早期评估中的价值与整合策略, 以期实现肿瘤治疗与心脏保护的双重目标。

关键词

乳腺癌, 人表皮生长因子受体2, 靶向治疗, 右心室功能, 超声心动图, 肿瘤治疗相关心脏功能障碍

Multimodality Echocardiographic Assessment of Right Ventricular Function after Dual-Targeted Therapy for Breast Cancer

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Abstract

Human epidermal growth factor receptor 2 (Human epidermal growth factor receptor 2, HER2)-positive breast cancer is highly aggressive, accounting for 15%~20% of all breast cancers. Dual HER2 blockade with trastuzumab and pertuzumab combined with taxane- and carboplatin-based chemotherapy (TCbHP) has markedly improved survival. Cancer therapy-related cardiac dysfunction (CTRCD) has become a critical issue. Traditional surveillance focuses on left ventricular ejection fraction, while the right ventricle (RV) is often overlooked. This review addresses mechanisms of RV injury and the value of multimodality echocardiography—including conventional indices, speckle-tracking strain, four-dimensional volumetric quantification, and 4D-RV-Volume combined with speckle-tracking imaging (STI)—in early detection of subclinical RV dysfunction.

Keywords

Breast Cancer, Human Epidermal Growth Factor Receptor 2, Targeted Therapy, Right Ventricular Function, Echocardiography, Cancer Therapy-Related Cardiac Dysfunction

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1. 引言

乳腺癌是全球女性发病率最高的恶性肿瘤[1] [2]。GLOBOCAN 2022 数据显示, 2022 年全球新发乳腺癌约 230.9 万例, 居女性恶性肿瘤首位, 占有癌症死亡病例的 6.9% [1]。基于 185 个国家的数据分析显示, 2022 年约新发乳腺癌 230 万例、死亡 67 万例, 预计至 2050 年年新发与死亡病例较 2022 年分别增长 38%和 68%, 全球女性乳腺癌疾病负担持续加重[3]。其中, 人类表皮生长因子受体 2 (Human epidermal growth factor receptor 2, HER2)阳性乳腺癌约占全部乳腺癌的 15%~20%, 以增殖活跃、侵袭性强为特征, 预后较差[4] [5]。

随着分子分型研究的深入, 精准治疗已成为改善不同亚型预后的关键策略。目前, 作为 HER2 阳性乳腺癌的标准治疗方案, 即以曲妥珠单抗(Trastuzumab)、帕妥珠单抗(Pertuzumab)为核心的双靶联合治疗方案显著改善了该亚型患者的临床结局[4] [6] [7], 显著提高患者的病理完全缓解率(Pathological complete response rate, pCR) [8]。PEONY 研究最终分析进一步证实, 双靶联合多西他赛的新辅助方案在亚洲人群中疗效确切、安全性可控[9]。尽管如此, 其导致的肿瘤治疗相关心脏功能障碍(Cancer therapy-related cardiac dysfunction, CTRCD)仍不容忽视[10]。在 50 岁以上的乳腺癌患者中, 肿瘤治疗的远期心血管疾病死亡风险甚至超过疾病本身[11] [12], 而靶向药物与化疗药物的协同毒性亦增加了心脏毒性风险[13] [14]。为了确保乳腺癌患者的远期预后, 2022 年欧洲心脏病学会(European Society of Cardiology, ESC)肿瘤心脏病学指南系统界定了 CTRCD 的诊断与分层标准, 强调基线评估与动态监测[10] [13] [15]。但现行 CTRCD 定义以左心室为核心, 右心室功能评估长期被忽视[16]。越来越多的证据表明化疗与靶向治疗均可引起右心室亚临床损伤, 这提示右心室亚临床损伤可能在左室功能异常之前即已发生, 且具有独立预后价值[16] [17]。

然而, 对于右心室功能评估来说, 常规超声参数虽适用于基线筛查, 但角度依赖性强, 对早期亚临

床损伤敏感性不足；二维及三维斑点追踪成像(Speckle-tracking imaging, STI)可定量分析心肌形变，较射血分数更早识别亚临床损伤；四维右室容积定量(Four-dimensional right ventricular volume quantitative analysis, 4D-RV-Volume)技术则实现了角度无关的动态容积定量，与心血管磁共振(Cardiac magnetic resonance, CMR)具有良好一致性[18]-[21]。将 4D-RV-Volume 与 STI 联合，可同时兼顾右心室“泵血能力”与“心肌形变”两个维度，有望实现对右室收缩功能的全面、动态评价[22]。然而，目前将 4D-RV-Volume 与 STI 联合应用于 HER2 阳性乳腺癌靶向治疗后右室功能评估的研究尚少，其临床价值有待系统总结。因此，本综述旨在梳理多模态超声在 HER2 阳性乳腺癌靶向治疗相关右室功能评估中的研究进展，以期临床早期识别 CTRCD、优化心脏保护策略提供参考。

2. HER2 阳性乳腺癌靶向治疗相关右室损伤的发生机制

HER2 (ErbB2)介导的信号通路在维持心肌细胞存活、调控能量稳态中发挥关键作用。心肌微血管内皮细胞分泌的神经调节蛋白-1 (Neuregulin-1, NRG-1)与 ErbB4 结合后，可促进 ErbB4/ErbB2 异二聚体形成，继而激活磷脂酰肌醇 3-激酶/蛋白激酶 B (Phosphoinositide 3-kinase/protein kinase B, PI3K/Akt)和细胞外信号调节激酶(Extracellular signal-regulated kinase, ERK)等下游通路，维持心肌细胞存活及线粒体功能[23][24]。曲妥珠单抗与帕妥珠单抗分别结合 HER2 不同表位，双靶联合更完整地阻断上述信号，削弱心肌细胞应对氧化应激的代偿能力[23]-[25]。TCbHP 方案(紫杉类 + 卡铂 + 曲妥珠单抗 + 帕妥珠单抗)作为当前 HER2 阳性乳腺癌新辅助/辅助治疗的优选方案[6]，其化疗骨架由紫杉类(多西他赛或紫杉醇)和卡铂组成[26][27]。紫杉类药物通过稳定微管蛋白促进活性氧(Reactive oxygen species, ROS)产生和线粒体功能障碍；卡铂通过脱氧核糖核酸(Deoxyribonucleic acid, DNA)交联产生氧化应激，导致线粒体损伤和钙超载[12]。在双靶治疗已削弱心肌细胞存活信号的基础上，紫杉类和卡铂通过上述途径可以直接损伤心肌细胞，形成协同毒性[12]。

右心室因其独特的解剖和生理特性，成为抗癌治疗相关心脏毒性中的“薄弱环节”。右心室室壁较薄、呈新月形、顺应性较高，对肺循环阻力和后负荷变化极为敏感；其收缩功能由纵向、径向和前后向运动共同完成，单一二维参数难以完整反映其功能状态；其冠状动脉血供以微血管灌注为主，储备能力有限，对内皮功能异常尤为敏感[16][28]。在 TCbHP 治疗背景下，双靶治疗阻断 NRG-1/ErbB 信号削弱心肌修复能力，紫杉类和卡铂的氧化应激与线粒体毒性直接攻击心肌细胞，加之左心室功能下降或化疗相关肺血管内皮损伤可升高右心室后负荷，上述损伤机制共同指向解剖易损的右心室，使其损伤风险不容忽视[16][22][28]。

而且，上述损伤机制与超声表现存在着对应关系。双靶治疗阻断 NRG-1/ErbB 信号、削弱心肌细胞存活及线粒体功能，与 STI 检测到的 RVGLS、RVFWS 早期下降相对应[16][23]-[25]；紫杉类经 ROS 蓄积、卡铂经 DNA 交联诱导的氧化应激与线粒体损伤，可能进一步表现为右心室心肌做功指数(GWI)降低及做功效率下降[12][29]；化疗相关肺血管内皮损伤或左心功能下降所致右心室后负荷增加，则可能表现为三尖瓣环收缩期位移(Tricuspid annular plane systolic excursion, TAPSE)下降及 4D-RV-Volume 检测到的节段收缩不同步[16][22][28]。不同治疗成分可能通过差异化路径损伤右心室，为选择针对性监测指标提供机制依据。

3. 右心室功能的多模态超声评估技术

3.1. 常规超声参数：基础与局限

三尖瓣环收缩期位移(TAPSE)、三尖瓣外侧瓣环收缩期峰值速度(Tricuspid annulus systolic blood flow velocity of tissues, S')、右心室面积变化率(Right ventricular fractional area change, RVFAC)是临床最常用的

右心室收缩功能指标。TAPSE 和 S'主要反映右心室游离壁基底段的纵向运动, RVFAC 则基于四腔心切面计算面积变化比例, 其中 RVFAC < 35%通常提示右心室收缩功能异常[20]。这些参数操作简便、重复性较好, 适用于基线筛查。然而, TAPSE 和 S'角度依赖性强, 仅反映局部纵向运动; RVFAC 未纳入右心室流出道, 且对早期亚临床损伤敏感性不足[20] [30]。因此, 常规参数正常并不能排除早期右心室功能损害。

3.2. 斑点追踪成像技术: 从二维到三维

斑点追踪成像技术(STI)通过追踪心肌声学斑点的位移定量分析心肌形变, 不依赖角度, 对亚临床心功能变化较常规参数更为敏感。右心室游离壁纵向应变(Right ventricular free-wall longitudinal strain, RVFWLS)和右心室整体纵向应变(Right ventricular global longitudinal strain, RVGLS)是评估右心室收缩功能的核心参数, 欧洲心血管影像协会/美国超声心动图学会(European Association of Cardiovascular Imaging/American Society of Echocardiography, EACVI/ASE)已发布标准化共识, 近期多厂商参考值研究虽进一步规范了正常范围, 但厂商间算法差异导致的测量互通性问题仍未完全解决(详见第 4 节) [18] [19] [22] [29] [31]。

在 HER2 阳性乳腺癌靶向治疗患者中, 二维 STI 已显示出早期识别右心室亚临床损伤的价值。Keramida 等[16]报道, 曲妥珠单抗治疗期间右心室整体纵向应变(RVGLS)与左心室整体纵向应变(Left ventricular global longitudinal strain, LVGLS)几乎同步恶化, 其识别心脏毒性的 cutoff 值为下降 14.8%。Calleja 等[17]发现, 发生心脏毒性的患者中 40%合并右心室应变异常。这说明了右心室作为薄弱环节易出现早期应变改变, 因此二维 STI 应作为右心室功能监测的常规手段[10] [32]。

三维斑点追踪(Three-dimensional speckle tracking, 3D-STI)进一步突破了二维切面的限制, 可在全容积数据基础上计算三维右心室整体纵向应变(Three-dimensional right ventricular global longitudinal strain, 3D-RVGLS), 减少几何假设和切面依赖。研究表明, 乳腺癌化疗患者中即使常规右心室指标尚未异常, 三维应变已可检测到早期亚临床功能减退[33] [34]。虽然相关研究多以蒽环类药物为基础, 但三维 STI 在检测早期心肌形变异常方面的敏感性提示, 其在 TCbHP 方案右心室监测中同样具有应用潜力[34]。

3.3. 三维与四维右室容积定量及联合 STI

右心室形态复杂、呈新月形, 二维切面和简化几何模型难以完整反映其容积和功能状态[28]。三维超声心动图(Three-dimensional echocardiography, 3DE)通过全容积数据采集与重建, 可获得角度无关的右心室射血分数(Three-dimensional right ventricular ejection fraction, 3D-RVEF)、舒张末期容积和收缩末期容积。以心血管磁共振为参照, 机器学习辅助的 3DE 自动分割技术可获得重复性较好的右心室容积和射血分数, 但部分病例仍需人工校正心内膜边界, 且存在低估右心室容积的倾向[21]。尽管如此, 3DE 与 CMR 的一致性已得到广泛验证, 为临床提供了可靠的右心室容积评估工具[21] [34]。

四维右室容积定量(4D-RV-Volume)技术是在 3DE 基础上的进一步拓展, 通过实时三维动态成像连续追踪整个心动周期中右心室整体及节段容积变化, 实现了时间维度上的动态容积定量。4D-RV-Volume 不仅能够提供与 CMR 高度一致的右心室射血分数和容积参数, 还可通过节段容积分析揭示右心室收缩的时空不同步性[21] [35]。这一技术克服了二维方法对切面和几何假设的依赖, 实现了从静态到动态、从整体到节段的跨越, 能够更精细地捕捉右心室收缩功能的细微变化[20] [21]。

右心室功能的完整评估需要同时兼顾“泵血能力”(容积变化)和“心肌形变”(应变分析)两个维度[22]。4D-RV-Volume 擅长量化右心室整体射血功能, 而 STI 则敏感地反映心肌纤维的缩短和伸长。两者联合可实现优势互补——4D-RV-Volume 提供精确、角度无关的容积和射血分数数据; STI 则提供游离壁和室间隔的纵向应变信息, 作为早期识别亚临床损伤的敏感标志。将容积与形变整合于一次超声检查中, 不

仅提高了评估的全面性,还减少了多次检查的变异性和患者负担[22]。在 TCbHP 方案治疗中,4D-RV-Volume 可精确追踪右心室容积动态变化,及时发现射血分数的亚临床下降;STI 则通过应变分析,在容积尚未明显变化时即可检测到心肌形变异常。两者联合,既能从宏观层面把握右心室泵血功能的演变,又能从微观层面揭示心肌损伤的早期信号[22][32]。此外,节段容积分析结合节段应变分析,可进一步揭示右心室不同部位对 TCbHP 方案毒性的反应差异,为理解损伤的空间分布特征提供信息[35]。

3.4. 心肌做功与血流动力学评估

应变指标虽对早期损伤敏感,但受前后负荷影响较大。基于无创血压构建的压力-应变环(Pressure-strain loop, PSL)将心肌形变与瞬时心室压力结合,可计算整体做功指数(Global work index, GWI)、做功效率(Global work efficiency, GWE)与无效功(Global wasted work, GWW),更贴近真实心肌收缩力,且相对负荷依赖性较低[29][36][37]。这一理念已从左心室拓展至右心室,初步研究表明右心室心肌做功可无创反映其收缩功能,并与有创压力-容积分析相印证[29][38]。然而,右心室心肌做功的参考值范围及在肿瘤治疗人群中的验证研究仍待完善,目前更适合作为探索性评估工具[29][36]。

矢量血流成像(Vector flow mapping, VFM)可直观显示涡流结构、能量损耗等血流动力学信息,从能量与流场角度补充心肌形变评估[39]。在肿瘤治疗相关心脏毒性评估中,VFM 有望更早发现右心室充盈与排空效率的改变,但其临床应用仍受图像质量限制,标准化程度尚低[40]。此外,人工智能(Artificial intelligence, AI)辅助分割技术可提升右心室自动定量分析的准确性和效率,为大规模临床监测提供了新的可能[41]-[43]。

在临床监测中,可以根据上述不同技术的优势采用分层递进的评估策略[10][32]:基线时建立完整的右心室功能档案(常规参数+二维 STI);治疗期间动态复查二维 STI,若发现异常则进一步行 4D-RV-Volume 联合 STI 检查;对于高危患者或出现右心室功能减退者,可纳入心肌做功或 VFM 进行机制探索。

4. 当前面临的挑战

当前右心室相关 CTRCD 的规范化临床应用仍面临多重挑战。其一,现行 CTRCD 定义仍以左心室为核心[10][44],右心室尚缺乏公认的功能异常分级和诊断标准,现有应变 cutoff 值[16]多来自单中心小样本研究,尚缺乏大规模前瞻性证据支持[21][30];其二,STI、心肌做功等形变类参数受厂商算法、探头频率影响明显,跨设备测量结果可比性差,标准化协作虽已开展,但厂商依赖问题尚未完全解决[18][22][32],制约了多中心数据整合与临床推广。其三,早期影像学改变对应的临床干预阈值尚不明确,右心室应变或容积下降至何种程度、何时启动心脏保护干预,目前证据不足[30][31];其四,CMR 作为右心室容积与功能评估的金标准,检查耗时长、费用高、部分患者存在检查禁忌[15][22],难以满足动态监测需求,凸显了超声技术在临床可及性上的替代与互补价值。

5. 小结与展望

多模态超声技术为 HER2 阳性乳腺癌 TCbHP 方案相关右心室功能评估提供了从基线筛查到早期识别、动态监测的完整工具链。常规参数适用于基线评估,二维及三维斑点追踪成像可更早识别心肌形变异常,4D-RV-Volume 技术则实现了角度无关的动态容积定量,与心血管磁共振具有良好一致性。将 4D-RV-Volume 与 STI 联合,可同时兼顾右心室“泵血能力”与“心肌形变”两个维度,契合 2022 年 ESC 肿瘤心脏病学指南所倡导的多参数动态监测理念[10][32]。

未来研究可从三方面深入:一是开发针对右心室的影像组学预测模型,整合灰阶纹理特征与多参数应变,构建心脏毒性早期预测工具[45];二是开展前瞻性、多中心研究,借鉴左心室应变指导心脏保护治

疗的 SUCCOUR 试验经验[46],明确右心室应变下降至何种幅度、何时启动干预及其对远期预后的影响;三是探索超声定量指标与新型生物标志物(如高敏肌钙蛋白、NT-proBNP)联合模型在心脏毒性监测中的增量价值[44]。最终,通过技术创新、证据积累与多学科协作,实现肿瘤治疗与右心室功能保护的双重目标。

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