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· 综 述 ·

# 肺功能成像在新型冠状病毒肺炎急性及康复期病变的研究进展



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**〔摘要〕** 截至2022年11月4日, 新型冠状病毒肺炎(coronavirus disease 2019, COVID-19)确诊病例超过6.28亿, 死亡人数超过657万。肺是COVID-19最常累及的器官, 主要表现为COVID-19肺炎、肺血栓栓塞等急性病变及康复期COVID-19相关小气道病变、肺间质纤维化。肺功能成像使用影像学成像技术对肺功能进行区域性可视化量化评估, 并额外提供常规肺功能检查未涉及的区域分布及定位信息。为全面了解肺功能成像技术在COVID-19患者中的应用价值, 本文归纳总结CT、MRI及核医学成像技术在COVID-19急性及康复期病变早期识别、诊断及随访中的初步应用, 并展望各种成像模态及相关技术在未来更广泛的应用。

**〔关键词〕** 新型冠状病毒肺炎; 功能成像; 肺血栓栓塞; 小气道病变; 肺间质纤维化

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## Research progress of pulmonary functional imaging in acute and convalescent lesions of COVID-19

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**〔Abstract〕** During the coronavirus disease 2019 (COVID-19) pandemic, more than 628 million people were diagnosed and more than 6.57 million died. The lung is the most frequently involved organ of COVID-19, which is mainly manifested as COVID-19 pneumonia and pulmonary thromboembolism in acute phase and COVID-19 related small airway disease and pulmonary interstitial fibrosis in convalescent phase. Pulmonary functional imaging uses imaging techniques for regional visual and quantitative assessment of lung function, providing additional regional distribution and location information, which cannot be provided by routine pulmonary function test. In order to fully understand the application value of pulmonary functional imaging in patients with COVID-19, this review summarizes the preliminary clinical application of CT, MRI and nuclear medicine imaging techniques in the early screening, diagnosis, and follow-up of acute and convalescent lesions in COVID-19, and looks forward to the wider application of various imaging modalities and related technologies in the future.

**〔Key Words〕** coronavirus disease 2019; functional imaging; pulmonary thromboembolism; small airway disease; pulmonary interstitial fibrosis

截至2022年11月4日, 世界卫生组织公布新型冠状病毒肺炎(coronavirus disease 2019, COVID-19)确诊病例超过6.28亿, 死亡人数超过657万<sup>[1]</sup>。随着新型冠状病毒的不断变异, 演化出阿尔法(Alpha)、贝塔(Beta)、伽玛(Gamma)、

德尔塔(Delta)和奥密克戎(Omicron)5种“关切变异株”(variant of concern, VOC)<sup>[2]</sup>。肺是COVID-19最常累及的器官, 虽然病毒传播能力不断增强, 但患者肺部感染率逐渐降低、症状逐渐减轻, 可能与病毒在肺部的复制能力减弱相关<sup>[3]</sup>。

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一项多中心尸检研究<sup>[4]</sup>发现, COVID-19 患者肺部病变以弥漫性肺泡损伤为主, 伴透明膜形成及Ⅱ型肺泡上皮细胞不典型增生; 87% (33/38) 的病例在肺小动脉 (直径<1 mm) 中存在与凝血障碍一致的血小板-纤维蛋白血栓, 这在 COVID-19 死亡患者中很常见。另一项对危重型 COVID-19 患者的尸检结果<sup>[5]</sup>也显示, 肺部有明显的血管病变和异常肺泡间隔充血水肿。以上病理改变在临床上主要表现为肺炎及肺血栓栓塞。COVID-19 患者康复后, 其肺功能仍可能存在不同程度受损, 表现为肺限制性通气功能障碍、小气道功能障碍以及弥散功能障碍等<sup>[6-7]</sup>, 是后新冠综合征 (post-COVID-19 syndrome) 或长新冠 (long COVID) 的重要表现之一。同样, 中国自新冠疫情暴发以来制定的《新型冠状病毒肺炎诊疗方案 (试行第七版至第九版)》<sup>[8-10]</sup>中, COVID-19 患者肺部病理改变也主要表现为肺炎、肺血栓栓塞、小气道病变以及肺间质纤维化。

肺功能成像定义为使用计算机断层扫描 (CT)、磁共振 (MRI) 和核医学成像技术对肺功能进行区域性可视化量化评估, 包括无创性标记及测量全肺通气、灌注、气体交换和生物力学等肺生理学参数。肺功能成像可额外提供常规肺功能检查 (PFT) 所不能提供的区域分布及定位信息<sup>[11]</sup>。为全面了解 CT、MRI 及核医学成像技术在 COVID-19 肺炎、肺血栓栓塞等急性病变及康复期 COVID-19 相关小气道病变、肺间质纤维化等早期识别、诊断及随访中的作用, 本文归纳总结肺功能成像在 COVID-19 急性及康复期的初步临床应用, 并进行展望。

## 1 COVID-19 急性期肺病变

1.1 COVID-19 肺炎 胸部 CT, 尤其是薄层 CT, 广泛用于 COVID-19 肺炎的筛查和诊断<sup>[12]</sup>。COVID-19 肺炎 CT 典型表现为双侧肺外周及下肺分布为主的多发磨玻璃密度影 (ground glass opacity, GGO)、伴或不伴实变、小叶间隔增厚 (铺路石征) 等<sup>[12-14]</sup>。尽管 CT 用于诊断 COVID-19 肺炎的特异度 (56%) 较低, 但灵敏度 (97%) 和准确性 (72%) 较高<sup>[15]</sup>, 有助于早期发现 COVID-19

肺炎, 并为其筛查、早期诊断和治疗提供重要依据。

多项研究<sup>[16-19]</sup>证实, 胸部 MRI 与 CT 对 COVID-19 特征性征象的识别具有较好或满意的一致性, 并且能提供额外的病理生理信息。Torkian 等<sup>[16]</sup>发现多个 MRI 序列与胸部 CT 在识别 COVID-19 肺炎多发 GGOs、实变、网状影及反晕征等征象方面具有较高一致性, 其中 T<sub>2</sub> 加权快速自旋回波-快速反转恢复序列 (TSE-TIRM-T<sub>2</sub>WI) 显示病变较其他序列更清楚, 尤其是继发于肺实质炎性病变的水肿区。Pecoraro 等<sup>[17]</sup>也证实胸部 MRI 与 CT 在评估 COVID-19 肺炎征象方面表现出极好的一致性, 同时观察到扩散加权成像 (DWI) 可用于评估 COVID-19 肺部炎症活动性。呼吸门控三维超短回波时间序列 (3D UTE) MRI 与常规 CT 的前瞻性对照研究显示, UTE-MRI 在识别 COVID-19 肺炎 GGOs、实变及铺路石征等典型征象上与 CT 具有高度一致性, 且不易受到 T<sub>2</sub>\* 信号快速衰减和呼吸运动的影响<sup>[18]</sup>。同样, 呼吸门控三维氧增强-超短回波时间序列 (3D OE-UTE) MRI 进一步可同时生成全肺通气图, 并发现病变区域肺通气功能减低<sup>[19]</sup>。尽管在 COVID-19 大流行期间, MRI 不推荐作为 COVID-19 肺炎的首选影像学检查, 但作为一种无电离辐射的成像方式, MRI 可成为儿童、孕妇及短时间内需多次随访肺部 CT 患者的替代方案<sup>[16]</sup>。

氟代脱氧葡萄糖正电子发射断层扫描/CT (FDG PET/CT) 作为一种解剖与功能相结合的影像学检查方法, 在评估炎症和感染性肺疾病方面也具有重要作用<sup>[20]</sup>。PET/CT 能够在细胞水平评估早期代谢及功能等分子信息<sup>[21]</sup>, FDG PET/CT 能进一步在细胞水平检测到炎性细胞葡萄糖利用增多<sup>[22]</sup>。<sup>18</sup>F-FDG 是最常用的示踪剂, <sup>18</sup>F-FDG PET/CT 可作为 COVID-19 肺炎的补充显示手段, 特别是在无症状、临床症状无特异性及鉴别诊断困难的早期阶段<sup>[23-24]</sup>。Qin 等<sup>[23]</sup>报道了 COVID-19 大流行早期, 4 例高度可疑的急性期无症状患者行 <sup>18</sup>F-FDG PET/CT 检查, 结果显示肺部 GGOs 和 (或) 实变等病灶呈高摄取。Dietz 等<sup>[25]</sup>对 13 例非危重型 COVID-19 患者出现症状后 6~14 d 行

$^{18}\text{F}$ -FDG PET/CT 检查,发现肺部病变  $^{18}\text{F}$ -FDG 摄取量均增加。Bai 等<sup>[26]</sup>对重型 COVID-19 康复患者行  $^{18}\text{F}$ -FDG PET/CT 检查,观察到残留肺部病变仍呈高代谢,存在明显炎症。尽管  $^{18}\text{F}$ -FDG PET/CT 检测 COVID-19 肺炎灵敏度高,但特异度较低、费用高、辐射剂量大及采集时间长,限制了核医学成像技术在 COVID-19 肺炎中的广泛临床应用<sup>[27]</sup>。

**1.2 COVID-19 肺血栓栓塞** CT在肺血栓栓塞的识别与诊断中具有重要价值。Lins 等<sup>[28]</sup>对 COVID-19 住院患者的高分辨率 CT (HRCT) 肺血管定量研究提示,肺血从小血管向大血管转移的“再分布”与直径低于 CT 分辨率的肺小血管阻力增加相一致,可能与微血栓栓塞和血管重塑相关。相较于常规 CT,双能 CT 灌注扫描 (DEPI) 可用于 CT 肺动脉成像 (CTPA),在不增加辐射剂量的情况下,同时评估是否存在肺动脉血栓和局部肺灌注异常<sup>[29]</sup>。Idilman 等<sup>[29]</sup>使用 DEPI 评估轻至重型 COVID-19 患者的肺灌注,发现 25.8% (8/31) 患者均存在肺灌注缺血区,其中 2 例经 CTPA 证实为肺栓塞,提示大部分轻至重型 COVID-19 患者的肺灌注缺血区可能与系统性微血栓有关。Grillet 等<sup>[30]</sup>在对重型 COVID-19 患者行肺 DEPI 时,尽管 34% (29/85) 患者未观察到明显肺动脉栓子,但其肺内也存在大量肺缺血区,这也可能与 COVID-19 相关微血栓形成有关。

灌注单光子发射计算机断层扫描/CT (Q-SPECT/CT) 是一种快速、高精度诊断急性肺栓塞的可靠方法,在诊断肺栓塞方面比通气/灌注成像准确性更高<sup>[31]</sup>。Ozturk 等<sup>[32]</sup>对低肺栓塞风险的轻型及普通型 COVID-19 患者行 Q-SPECT/CT, 36.6% (28/77) CT 无异常者发现肺灌注缺血区,提示即使轻型及普通型 COVID-19 患者也有肺血栓形成。Das 等<sup>[33]</sup>也发现 67% (4/6) 肺栓塞中、高危险度的重型及危重型 COVID-19 患者 Q-SPECT/CT 呈阳性表现。Q-SPECT/CT 可用于检测外周小肺动脉血栓且灵敏度高,因此可能对 COVID-19 所致肺小动脉血栓栓塞也有临床诊断价值。

## 2 COVID-19 康复期肺病变

### 2.1 COVID-19 肺小气道病变 吸气/呼气双气

相 CT 作为一种无创、高灵敏度的肺功能成像检查,可以用于早期发现空气滞留与小气道病变。Fleischner 协会将空气滞留定义为病理生理学气道阻塞 (通常是不完全阻塞) 导致肺远端空气潴留。CT 上空气滞留表现常用于评估肺小气道病变,肺小气道病变是指直径  $\leq 2\text{ mm}$  的气道病变。吸气/呼气双气相 CT 有助于识别空气滞留<sup>[34]</sup>。Franquet 等<sup>[35]</sup>对出院 1 个月后仍伴有持续呼吸道症状的后新冠综合征患者行吸气/呼气双气相 CT 检查发现,77% (37/48) 患者存在空气滞留,高度提示合并小气道病变。另一项吸气/呼气双气相 HRCT 评估 COVID-19 小气道病变多中心研究<sup>[36]</sup>显示,32.4% (35/108) 患者存在空气滞留,并持续存在于 2 个月的随访中。Jia 等<sup>[37]</sup>也发现 6 个月随访时的定量吸气/呼气双气相 CT 中,肺弥散功能受损的 COVID-19 患者容易出现空气滞留,可能与小气道损伤有关。一项前瞻性研究<sup>[38]</sup>显示,在初始感染后随访 200 d 的 9 例 COVID-19 患者中,89% (8/9) 的患者仍能在吸气/呼气双气相 CT 上观察到空气滞留。因此,推测 COVID-19 患者的小气道病变可能会持续存在较长时间。在这种情况下,可以适当延长此类患者的 CT 随访间隔时间,并采取基于迭代重建算法的低剂量 CT 扫描方案,既减少了不必要的辐射剂量,又减轻了患者的经济和心理负担<sup>[35-36]</sup>。

MRI 能量化评估肺通气的区域异质性,也可用于早期发现小气道病变。相位分辨肺功能 (PREFUL) MRI 可用于动态量化区域通气,较静态通气图对肺功能异常更敏感,采取 PREFUL 法的肺自由呼吸  $^1\text{H}$ -MRI 通过对 COVID-19 康复患者区域通气的可视化和量化评估,发现其存在显著高于健康人的区域异质性高通气区<sup>[39]</sup>。MRI 通气障碍百分比 (VDP) 可反映小气道异常,Kooner 等<sup>[40]</sup>发现无论住院与否,康复后持续存在症状的 COVID-19 患者超极化氙气 MRI ( $^{129}\text{Xe}$ -MRI) 的 VDP 均增高,且有住院史的患者 VDP 更高,提示感染后持续存在的症状可能与小气道病变有关。因此,MRI 在 COVID-19 康复期小气道病变早期发现及随访中具有潜在及广泛的临床应用价值。

### 2.2 COVID-19 肺间质纤维化 肺部 CT, 尤其

HRCT, 是评估间质性肺疾病灵敏度较高的影像学检查。Yang 等<sup>[41]</sup>发现 46% (76/166) 的住院 COVID-19 患者在恢复早期 (出现症状后 56 d) 的随访 CT 有纤维化表现, 其中 89% (68/76) 的患者纤维化改变位于外周, 与 GGOs 和实变分布一致, 提示炎症的恢复过程<sup>[41]</sup>。Froidure 等<sup>[42]</sup>对重型及危重型 COVID-19 患者进行 3 个月随访, 发现 21% (22/107) 的患者 HRCT 上有纤维化征象, 47% (58/122) 的患者肺一氧化碳弥散量 (DLCO) 降低。Jutant 等<sup>[43]</sup>也发现 19.3% (33/171) 的患者随访 4 个月后 HRCT 上仍可见轻度肺纤维化。Jia 等<sup>[37]</sup>进一步证实 COVID-19 康复患者在 6 个月随访时, 在定量双气相 CT 仍可见纤维化表现, 并较基线 CT 增加。

MRI 可以早期发现 COVID-19 所致肺间质损伤的肺功能改变。<sup>129</sup>Xe-MRI 是一种能够评估通气、微结构和气体交换的独特技术<sup>[44]</sup>, 可通过红细胞相对于组织和血浆中的氙信号比值 (RBC/TP) 来评估肺功能和气体交换, 比值降低表明肺内气体交换受损<sup>[45]</sup>。肺间质损伤可能导致 DLCO 降低<sup>[46]</sup>。Li 等<sup>[44]</sup>首次将 <sup>129</sup>Xe-MRI 用于评估 COVID-19 引起的肺损伤, 发现其较健康个体有更高的 VDP (5.9% vs 3.7%,  $P=0.039$ ), 且尽管肺微结构不变, 但气血交换功能减弱, 气血交换时间延长 (43.5 ms vs 32.5 ms,  $P=0.038$ ), RBC/TP 减低 (0.279 vs 0.330,  $P=0.041$ )。Grist 等<sup>[47]</sup>也发现 COVID-19 肺炎康复出院 3 个月后仍呼吸困难的患者, 尽管其 CT 表现正常或接近正常且 DLCO 在正常范围内, <sup>129</sup>Xe-MRI 仍显示 RBC/TP 较健康受试者减低 [(0.3±0.1) vs (0.5±0.1),  $P=0.001$ ], 肺内气体转移异常, 肺泡毛细血管扩散受限。因此, <sup>129</sup>Xe-MRI 在检测 COVID-19 所致肺损伤方面, 可能是一种比 PFT (包括 DLCO) 更敏感的方法, 能更好地解释后 COVID-19 综合征患者的呼吸困难<sup>[47]</sup>。另一项对首次感染后 ≥5 个月的非住院及住院 COVID-19 患者的前瞻性研究<sup>[48]</sup>进一步证实, 尽管 CT 表现正常, <sup>129</sup>Xe-MRI 仍显示健康受试组 RBC/TP 显著高于住院组 [(0.45±0.07) vs (0.31±0.10),  $P=0.02$ ] 与非住院组 [(0.45±0.07) vs (0.37±0.10),  $P=0.03$ ], 且非住院组 DLCO

低于住院组 [(76%±8%) vs (86%±8%),  $P=0.04$ ]。<sup>129</sup>Xe-MRI 在评估 COVID-19 患者肺气体交换功能方面可作为胸部 CT 的有力补充, 并可用于患者在疾病进展和肺功能恢复期间的纵向随访。

### 3 小结及展望

本综述归纳总结了 CT、MRI 及核医学等肺功能成像方法在 COVID-19 肺炎、肺血栓栓塞等急性病变及 COVID-19 相关小气道病变、肺间质纤维化等康复期异常早期识别、诊断及随访中的初步临床应用。尽管这些基于多种成像技术的肺功能成像的持续进步可提供丰富的信息, 但肺功能成像图像采集时间较长、图像质量有待提高以及不同成像协议、不同成像仪器导致的图像差异, 限制了其在临床的进一步推广应用<sup>[49]</sup>。人工智能, 尤其是深度学习技术, 可以优化图像采集时间、提高图像质量并缩小图像差异, 有望加速肺功能成像在 COVID-19 相关肺损伤的临床转化与应用<sup>[49]</sup>。肺功能成像与人工智能的联合, 有助于全面理解 COVID-19 相关肺通气、灌注及气体转移异常等相关病理生理学机制, 并在 COVID-19 相关肺功能性损伤的定量、区域分布及可视化评估、动态随访中发挥重要作用。

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