

慢性阻塞性肺疾病患者膈肌功能障碍研究进展

谭 淦¹, 雷明盛^{2*}

¹湖南师范大学附属张家界医院, 湖南 张家界

²张家界市人民医院呼吸与危重症医学科, 湖南 张家界

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摘 要

慢性阻塞性肺疾病(COPD)作为一种以气流受限为主要表现的慢性呼吸系统疾病, 全球范围内患病率和致死率均居高不下。膈肌作为主要呼吸肌, 其功能障碍在COPD患者中普遍存在, 严重影响呼吸效率, 导致患者呼吸困难加重和生活质量下降。当前, 关于COPD患者膈肌功能障碍的病理机制尚未完全明确, 诊断手段也存在一定局限性, 给临床治疗带来挑战。近年来, 随着药物治疗、呼吸康复训练、机械辅助通气技术及新兴干预方法的发展, 膈肌功能的改善取得了显著进展。本文系统综述了COPD患者膈肌功能障碍的发病机制、诊断技术以及多种治疗策略的最新研究成果, 重点分析各类治疗方法的优势与不足, 旨在为临床实践提供理论支持和指导, 推动COPD膈肌功能障碍的精准治疗和患者预后改善。

关键词

慢性阻塞性肺疾病, 膈肌功能障碍, 治疗进展, 呼吸康复, 机械通气

Research Progress on Diaphragm Function Impairment in Patients with Chronic Obstructive Pulmonary Disease

Gan Tan¹, Mingsheng Lei^{2*}

¹Zhangjiajie Hospital Affiliated to Hunan Normal University, Zhangjiajie Hunan

²Respiratory and Critical Care Medicine Department, Zhangjiajie People's Hospital, Zhangjiajie Hunan

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Abstract

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease characterized

*通讯作者。

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primarily by airflow limitation, with high prevalence and mortality rates worldwide. The diaphragm, as the main respiratory muscle, commonly exhibits dysfunction in COPD patients, severely affecting respiratory efficiency and leading to increased dyspnea and decreased quality of life. Currently, the pathological mechanisms underlying diaphragm dysfunction in COPD patients are not fully understood, and diagnostic techniques have certain limitations, posing challenges for clinical therapeutics. In recent years, significant progress has been made in improving diaphragm function with the development of drug therapy, respiratory rehabilitation training, mechanical ventilation techniques, and emerging intervention methods. This article systematically reviews the latest research findings on the pathogenesis, diagnostic techniques, and various management strategies for diaphragm dysfunction in COPD patients, focusing on analyzing the advantages and disadvantages of different treatment methods, aiming to provide theoretical support and guidance for clinical practice, and promote precise treatment and improved prognosis for diaphragm dysfunction in COPD.

Keywords

Chronic Obstructive Pulmonary Disease, Diaphragm Dysfunction, Treatment Progress, Respiratory Rehabilitation, Mechanical Ventilation

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1. 引言

慢性阻塞性肺疾病(COPD)作为全球范围内主要的慢性呼吸疾病之一,其发病率和死亡率近年来持续上升,严重威胁着公共健康安全。根据 2017 年全球疾病负担研究数据显示,全球约有 5.45 亿人患有慢性呼吸疾病,其中 COPD 是导致死亡的第三大原因,2017 年死亡人数达到约 391 万人,较 1990 年增加了 18%。COPD 的发病率在不同地区存在较大差异,既受到遗传因素的影响,也与年龄、性别、体质指数、肥胖程度和身体活动量等个体因素有关,同时环境因素如吸烟、室内外空气污染和职业暴露也起着重要作用[1][2]。中国作为人口大国,COPD 的患病率持续处于高水平,其相关死亡风险也日益凸显[3]。此外,COPD 患者常伴有多种合并症,如冠心病、糖尿病和睡眠障碍等,进一步加重了疾病负担[4][5]。COPD 的病理生理特征主要表现为持续的气流受限和气道炎症,导致肺功能逐渐恶化。除气道和肺组织病变外,COPD 还涉及呼吸肌,特别是膈肌的功能障碍。膈肌作为人体的主要呼吸肌,其结构和功能异常在 COPD 患者中普遍存在,并直接影响呼吸力学和换气效率。膈肌功能障碍表现为肌肉萎缩、收缩力减弱、耐力下降及运动时疲劳等,进而加剧呼吸困难、加重通气不足,甚至诱发呼吸衰竭[6]。传统的 COPD 治疗主要聚焦于控制气道炎症、缓解气道阻塞和预防急性加重,如吸入性支气管扩张剂、糖皮质激素、抗生素等药物治疗。然而,对于膈肌功能障碍的诊断和治疗尚未形成系统化和标准化的方案。因此,系统性认识 COPD 中膈肌功能障碍的病理机制及其临床意义,对于改善患者预后具有重要价值。

2. 生理病理机制

2.1. 结构和功能的改变

COPD 患者膈肌功能障碍的核心病理机制是膈肌的结构和功能的显著改变。COPD 导致膈肌肌纤维类型发生明显的转变,表现为快肌纤维比例增加而慢肌纤维减少,这种改变影响了膈肌的耐力,导致其

疲劳易发生[7]。慢性肺气肿和肺过度膨胀使膈肌受到机械性拉伸, 表现为膈肌扁平化和肌肉纤维萎缩。多项研究观察到 COPD 患者膈肌厚度减小、运动幅度降低, 且这些改变与肺功能下降密切相关[8]-[10]。此外, COPD 患者膈肌肌肉血流灌注减少, 营养不良加剧膈肌的功能下降, 导致肌肉力量和耐力减弱[11]。长期吸烟暴露可引起膈肌肌纤维的重塑和肌纤维直径缩小, 伴随内质网应激及凋亡信号的激活, 进一步加剧膈肌萎缩[12][13]。因此, COPD 通过肌纤维类型转变、形态学改变和肌肉营养不良等多种机制导致膈肌结构和功能的综合损害, 成为膈肌功能障碍的基础。

2.2. 呼吸力学异常与膈肌负荷增加

COPD 患者气流阻塞导致肺内气体滞留, 肺过度膨胀, 增加了膈肌的负荷, 使得其收缩效率明显降低。气流受限使得膈肌处于机械不利的位置, 膈肌扁平化降低其张力生成能力, 进而影响呼吸力学[9]。呼吸肌疲劳机制在 COPD 膈肌功能障碍中起重要作用, 疲劳的膈肌表现为力量减弱和耐力下降。此外, 神经肌肉传导异常和肌肉代谢紊乱加重膈肌疲劳。磁共振成像和超声研究表明, COPD 患者膈肌的运动能力和厚度均显著降低, 且这些指标与肺功能和疾病严重程度呈负相关[14]。神经肌肉方面, 跨颅磁刺激研究揭示 COPD 患者膈肌运动皮层兴奋性异常, 显示中枢神经系统对膈肌的调控受损, 可能加重呼吸肌疲劳[15]。因此, 呼吸力学异常和膈肌负荷增加是 COPD 膈肌功能障碍的重要机制, 氧化应激和神经肌肉传导异常共同参与膈肌疲劳的发展。

2.3. 分子机制

COPD 膈肌功能障碍机制包括氧化应激介导的肌肉蛋白质降解、线粒体功能障碍及能量代谢紊乱, 蛋白质合成与分解失衡, 炎症反应参与其中, 共同推动膈肌萎缩和收缩功能下降。

氧化应激通过蛋白质氧化、蛋白酶激活和钙敏感性降低, 促进肌肉细胞凋亡和蛋白质降解, 导致膈肌萎缩[16]-[18]。泛素-蛋白酶体系统活性增强是导致肌肉蛋白降解增加的主要途径之一, 相关的基因如 Trim63 和 Fbxo32 表达显著上调, 提示蛋白质合成与分解的失衡[COPD 膈肌功能障碍的分][19][20]。此外, 线粒体功能障碍及能量代谢异常也是膈肌功能减退的重要分子基础。COPD 患者膈肌线粒体显示呼吸链复合物活性降低、线粒体结构异常和氧化损伤加重, 伴随线粒体动力学蛋白如 DRP1 的表达上调, 导致线粒体分裂异常, 从而降低膈肌收缩能力和耐疲劳性[21]。

COPD 的全身性炎症状态会促使肌肉蛋白降解和功能障碍, 显著影响膈肌功能。慢性炎症介质如肿瘤坏死因子- α (TNF- α)、白细胞介素-6 (IL-6) 在膈肌肌肉细胞凋亡和代谢异常中发挥关键作用[22]。血液和肺组织中的炎症细胞浸润加重膈肌的炎症反应, 导致肌肉萎缩和力量减弱[23][24]。部分研究发现, COPD 患者膈肌中自噬及凋亡相关信号通路异常激活, 提示炎症驱动细胞死亡机制参与膈肌损伤[25][26]。

2.4. 慢性缺氧与营养不良

COPD 患者常伴慢性缺氧和营养不良, 这两者显著影响膈肌功能, 削弱呼吸能力和生活质量。慢性缺氧是 COPD 进展中的常见病理状态, 主要由于气体交换功能受损, 导致组织供氧不足[27]。缺氧诱导因子 1- α (Hypoxia-inducible factor 1- α , HIF-1 α) 在 COPD 患者的肺组织中显著上调, 促进慢性炎症和血管重塑, 同时导致骨骼肌代谢异常和功能下降[28]-[30]。慢性缺氧还通过氧化应激加剧肌肉损伤, COPD 患者膈肌及骨骼肌中氧化应激明显, 导致能量代谢受损[31]。此外, 慢性缺氧诱导的促炎细胞因子升高可导致膈肌组织损伤, 影响神经肌肉传导, 降低呼吸肌的神经驱动力, 进而减弱膈肌收缩能力。临床研究显示, COPD 患者在缺氧状态下, 呼吸中枢氧合度下降, 影响呼吸调节功能及呼吸肌耐力[32]。同时, 慢性缺氧与血管重塑和肺动脉高压相关, 增加呼吸负担, 加重膈肌疲劳[33][34]。

营养不良在 COPD 患者中极为常见, 流行病学数据显示约 20%至 60%的 COPD 患者存在不同程度的营养不良, 且与疾病严重程度密切相关[35]-[37]。营养不良通过多种机制加重膈肌功能障碍。营养不良会显著降低骨骼肌质量和力量, 包括膈肌在内的呼吸肌同样受累。在营养不良的 COPD 患者中, 脂肪自由质量指数、肌肉厚度及肌肉力量指标明显降低, 表现为肌肉萎缩和肌力减退[38]-[40]。营养不良还可导致能量代谢紊乱, 限制了肌肉的代谢活性和收缩能力, 引起肌肉疲劳和耐力下降[41][42]。此外, 营养不良能够增加炎症水平, 促进肌肉蛋白降解和细胞凋亡, 影响免疫功能。临床数据显示, 营养不良与住院时间延长及死亡率升高相关, 强调了营养状态对预后的重要性[35][43]。

3. 诊断技术进展

3.1. 影像学

膈肌作为呼吸的关键肌肉, 其功能障碍直接影响患者的呼吸效率和生活质量。影像学评估技术因其无创、直观的特点, 在膈肌功能障碍的诊断中发挥着重要作用。超声技术已成为临床评估膈肌运动的重要手段, 能够实时监测膈肌运动幅度及厚度, 具有便携、无辐射、重复性好的优势。多项研究表明, 超声测量膈肌在呼气末和吸气末的厚度及其厚度变化率可以有效反映膈肌的收缩功能, 且对 COPD 患者膈肌功能的评估具有较高的敏感性和特异性[14][44]。一项针对健康人群的研究提供了膈肌厚度、运动幅度及相关参数的正常参考范围, 并分析了性别、年龄、体重指数等因素对膈肌超声参数的影响, 为临床判断提供了重要依据[45]。此外, 磁共振成像(MRI)和计算机断层扫描(CT)则主要用于膈肌形态及运动功能的定量分析。MRI 不仅能提供膈肌的结构信息, 还能结合肺容量变化评估膈肌的动态运动功能, 在肌萎缩症等疾病中显示出重要价值[46]。CT 影像通过重建膈肌轮廓, 结合低衰减体积指标, 能够准确分析 COPD 患者膈肌运动模式的异常及其与肺部病变的关联[47]。近年来, 动态胸部 X 线摄影(Dynamic Chest Radiography, DCR)技术也逐渐应用于膈肌功能评估, 能够快速、动态地反映膈肌的运动状态, 且具有良好的患者耐受性[48]。此外, 深度学习和人工智能技术已开始应用于膈肌影像的自动分割与分析, 提高了诊断的客观性和准确性[49][50]。综合肺功能检测与影像学评估相结合, 能够提高膈肌功能障碍的诊断准确性, 为疾病的早期识别和治疗方案制定提供有力支持。

3.2. 呼吸力学与肌电图

呼吸力学参数和肌电图检测是评估膈肌功能的重要手段, 尤其在动态监测和功能评估中发挥着不可替代的作用。膈肌压力测定通过评估跨膈肌压差, 反映膈肌的收缩力量和功能状态, 为判断呼吸肌疲劳和功能障碍提供了直接指标[51]。膈肌电活动的监测是通过表面肌电图(surface electromyography, sEMG)技术实现的, 其无创性和连续监测能力使其在临床应用中日益广泛[52]。sEMG 不仅可以实时反映膈肌的活动水平, 还能评估肌肉疲劳状态及神经支配情况, 为机械通气患者的呼吸肌保护提供指导[53]。然而, sEMG 在实际应用中存在心脏肌电信号干扰等技术难点, 近年来, 先进的信号处理算法和质量控制标准的引入显著提升了 sEMG 数据的准确性和可靠性[54]。结合呼吸力学指标, 如膈肌压力、呼吸频率和潮气量等, 可实现对膈肌功能的动态评估, 帮助临床医生判断患者的呼吸努力程度及呼吸肌功能状态[55]。此外, 肌电图联合呼吸力学参数对机械通气患者的脱机成功率预测具有较高的临床价值, 有助于优化呼吸机支持和制定个体化康复方案[56]。在特定疾病如单侧膈肌功能障碍时, 肌电图监测还揭示了代偿性呼吸肌的激活模式变化, 提示额外呼吸肌的参与和功能调整[57]。总体而言, 呼吸力学与肌电图的联合应用为膈肌功能障碍的评估提供了多维度的数据支持, 促进了诊断的精细化和个体化治疗策略的制定。

3.3. 生物标志物与分子诊断

随着分子医学的发展, 生物标志物和分子影像学技术在膈肌功能障碍的诊断中展现出潜在的应用价

值。炎症因子及肌肉代谢相关标志物的研究为了解膈肌病理机制和早期诊断提供了新视角。COPD 等慢性疾病导致的系统性炎症状态与膈肌肌肉结构和功能改变密切相关, 相关炎症因子水平的变化可作为膈肌功能障碍的辅助诊断指标。此外, 在肌营养不良症等神经肌肉疾病中, 肌肉纤维的退行性变化与特异性蛋白质表达异常有关, 这些分子标志物的检测有助于早期识别膈肌损伤[44][58]。分子影像学技术, 如基于特异性探针的 MRI 和 PET 扫描, 能够实现对膈肌微观结构和代谢活动的无创观察, 辅助早期功能异常的识别[59]。未来, 多模态诊断策略将通过整合影像数据、生物标志物及呼吸功能参数, 实现对膈肌功能障碍的高敏感性和高特异性诊断, 有望推动精准医疗在该领域的应用。同时, 结合人工智能技术对多源数据进行深度分析, 将进一步提升诊断效率和准确度, 为膈肌功能障碍的早期干预和治疗提供科学依据。

4. 治疗进展

4.1. 药物治疗策略

慢性阻塞性肺疾病(COPD)患者膈肌功能障碍的药物治疗策略主要通过减轻气道阻塞和炎症反应, 从而间接改善膈肌功能。支气管扩张剂和抗炎药物是当前治疗 COPD 的基础药物, 它们通过扩张气道、减少炎症反应, 缓解肺部负担, 从而降低膈肌的负荷, 改善其功能。此外, 膈肌功能障碍的发生与氧化应激密切相关, 研究新型肌肉保护剂及抗氧化药物, 理论上可以减缓膈肌肌纤维的损伤和疲劳。营养支持与代谢调节药物也被认为有助于膈肌功能的恢复。一项针对富含植物化学物质饮食的研究发现, 高摄入量的植物化学物质与 COPD 患者呼吸功能和肌肉功能改善相关, 提示营养干预是辅助膈肌功能恢复的重要策略[60]。总体来看, 药物治疗策略不仅着眼于缓解气道阻塞和炎症, 更关注氧化应激和代谢异常对膈肌的影响, 力图通过多途径保护和改善膈肌功能, 减缓疾病进展。

4.2. 呼吸康复与物理治疗

呼吸康复和物理治疗在 COPD 患者膈肌功能障碍的治疗中发挥着越来越重要的作用。呼吸肌训练, 尤其是利用膈肌训练器进行的专项训练, 能够增强膈肌力量和耐力, 改善呼吸效率。吸气肌训练已被证实能显著提升最大吸气压、膈肌厚度及 6 分钟步行距离, 减轻呼吸困难, 改善生活质量[61]。具体而言, 吸气肌训练通过增加膈肌负荷, 刺激肌肉纤维增粗和肌肉力量增强, 显著提升最大吸气压力和膈肌厚度[62]。结合呼气肌训练的综合呼吸肌训练, 可以进一步协调膈肌及辅助呼吸肌群的功能, 提高整体呼吸肌群的协同工作效率。有氧运动与力量训练相结合的综合训练方案不仅提升整体呼吸功能, 还能改善患者的运动耐力和生活质量[63]。运动训练还可增强肌浆网功能, 通过上调肌浆网钙 ATP 酶的表达, 改善钙离子的释放和再摄取, 优化膈肌收缩和松弛效率[64]。此外, 物理治疗技术如电刺激, 尤其是呼吸神经肌肉电刺激(Respiratory neuromuscular electrical stimulation, RNES), 通过选择性激活 II 型肌纤维, 促进膈肌收缩, 改善肺容量和通气功能, 已显示出在稳定期 COPD 患者中的应用潜力[65][66]。电刺激可作为社区康复的一种可行、经济的辅助治疗手段, 显著提高运动能力和生活质量。物理治疗通过综合训练和电刺激等措施, 有效促进膈肌肌肉再生和功能恢复, 成为 COPD 膈肌功能障碍康复治疗的重要组成部分。

4.3. 机械辅助通气及新兴技术

机械辅助通气是缓解 COPD 患者膈肌负担、改善通气功能的关键手段。无创机械通气(Non-invasive mechanical ventilation, NIV)通过减轻膈肌负担, 改善血气指标和呼吸效率, 已被广泛应用于 COPD 急性加重和慢性期管理中[67][68]。研究表明, NIV 可有效提高膈肌厚度和厚度分数, 改善呼吸肌功能, 降低动脉二氧化碳分压[68][69]。侵入性机械通气虽为严重呼吸衰竭患者的重要救治手段, 但其对膈肌功能的

影响复杂, 过度依赖机械通气可能导致膈肌功能退化。针对这一问题, 顺序性肌肉训练结合机械通气被证明能促进膈肌功能恢复, 提高脱机成功率[62]。在新兴技术方面, 膈肌起搏器和干细胞治疗等干预手段正在积极探索中。膈肌起搏器可以通过电刺激维持或恢复膈肌收缩功能, 适用于部分严重膈肌功能障碍患者, 但仍处于临床研究阶段。干细胞治疗通过促进膈肌组织修复和再生, 有望成为未来治疗膈肌功能障碍的新途径[70]。这些新兴技术的应用前景广阔, 未来有望与传统机械辅助通气和康复治疗结合, 形成综合治疗体系, 进一步改善 COPD 患者膈肌功能和呼吸状况。

5. 结论

慢性阻塞性肺疾病患者膈肌功能障碍作为疾病进展和预后的关键影响因素, 近年来受到了越来越多的关注。膈肌功能障碍的病理基础复杂多样, 涉及肌肉结构的不可逆性改变、呼吸力学异常、氧化应激、系统性炎症反应、慢性缺氧与营养不良的相互作用。在诊断技术领域, 传统的呼吸力学检测与影像学技术相结合, 为膈肌功能障碍的早期发现提供了可靠手段。诸如超声膈肌厚度测量、MRI 定量评估及分子生物标志物的应用, 正在逐渐实现从结构到功能、从宏观到微观的精准诊断。然而, 不同研究在技术敏感性和特异性上的差异表明, 当前尚无单一金标准诊断工具。未来, 跨学科融合先进影像技术与分子诊断手段, 将是提升诊断准确性和早期干预效果的关键。在治疗方面, 药物干预、呼吸康复和机械辅助通气等多样化策略均显示出改善膈肌功能和临床症状的积极作用。特别是呼吸康复训练, 通过增强膈肌力量和耐力, 显著提高患者的运动耐量和生活质量。同时, 新兴技术如膈肌电刺激和干细胞治疗等, 尽管目前处于探索阶段, 但展现出广阔的应用前景。需要指出的是, 不同患者的病理状态和个体差异决定了治疗反应的多样性。如何根据具体病情制定个体化治疗方案, 是未来临床实践中的重要挑战。

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