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西维来司他钠联合俯卧位通气治疗ARDS：对氧合、炎症及生存获益的系统综述

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摘　要

急性呼吸窘迫综合征(ARDS)是一种严重的肺部炎症性疾病，具有高发病率和高死亡率。近年来，西维来司他钠联合俯卧位治疗在ARDS患者中的应用引起了广泛关注。本文综述了西维来司他钠联合俯卧位通气治疗ARDS患者的价值。通过分析国内外相关研究，探讨该联合治疗的作用机制、临床疗效及安全性，为ARDS的治疗提供了新的思路和依据。

关键词

急性呼吸窘迫综合征，西维来司他钠，俯卧位通气

Sivelestat Sodium Combined with Prone Position Ventilation in the Treatment of ARDS: A Systematic Review of Oxygenation, Inflammation, and Survival Benefits

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Abstract

Acute respiratory distress syndrome (ARDS) is a severe inflammatory lung condition associated

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with high incidence and mortality rates. In recent years, the combined use of sivelestat sodium and prone positioning in the management of ARDS has garnered increasing attention. This article reviews the clinical value of sivelestat sodium combined with prone position ventilation for treating ARDS patients. By synthesizing evidence from relevant studies conducted both domestically and internationally, it explores the mechanistic basis, therapeutic efficacy, and safety profile of this combined intervention, thereby offering new perspectives and evidence to inform ARDS treatment strategies.

Keywords

Acute Respiratory Distress Syndrome, Sivelestat Sodium, Prone Position Ventilation

1. 前言

急性呼吸窘迫综合征(Acute Respiratory Distress Syndrome, ARDS)是由肺内因素(如严重肺部感染、误吸、肺挫伤、淹溺、毒性气体吸入、放射性损伤)和肺外因素(如脓毒症(占比 ＞50%)、严重创伤、急性重症胰腺炎、大量输血、弥散性血管内凝血、神经源性肺水肿)引发的急性呼吸衰竭[1]-[3]。作为重症监护病房(Intensive Care Unit, ICU)常见危重症，其核心病理生理机制为失控性炎症反应介导的级联反应：肺泡－毛细血管屏障破坏→非心源性肺水肿→气体交换障碍，最终进展为顽固性低氧血症，显著增加多器官功能障碍综合征(Multiple Organ Dysfunction Syndrome, MODS)风险[4]-[6]。ARDS 呈现显著的疾病负担及人群异质性特征：占 ICU 住院患者的 10.4% [7]，全球发病率存在显著地域差异(1~86 例/10 万人/年)，其中欧美国家报告率较高[8]。COVID-19 大流行导致 ARDS 发病率激增 10 倍[9]。其预后险峻，28 天死亡率达 34.8%，院内总死亡率约 39% [9] [10]；死亡风险与多器官衰竭及低氧血症严重程度呈正相关[11]。尽管肺保护性通气策略和俯卧位通气(Prone Position Ventilation, PPV)已成为标准治疗，但患者死亡率仍高居不下，西维来司他钠(Sivelestat Sodium)作为选择性中性粒细胞弹性蛋白酶抑制剂(NE)，通抑制炎症级联反应减轻肺损伤。本综述旨在探讨西维来司他钠联合俯卧位通气治疗 ARDS 的潜在协同机制及其对氧合、炎性指标及预后的影响，以期为临床精准治疗提供新思路。

2. 西维来司他钠治疗 ARDS

2.1. 西维来司他钠的作用机制

西维来司他钠的核心作用机制在于特异性抑制 NE 活性，从而减轻由 NE 介导的组织损伤。NE 可降解弹性蛋白、胶原等细胞外基质，并激活炎症因子(如白细胞介素-8 (IL-8)、肿瘤坏死因子-α (TNF-α)))，从而诱导组织损伤和炎症级联反应[12]-[15]。

此外，西维来司他钠调控关键的炎症信号通路：

① 抑制 PI3K/AKT/mTOR 通路活性，下调该通路减少炎症因子释放，进而改善脓毒症相关的急性肺损伤(ALI) [16]；

② 激活细胞外信号调节激酶 1/2 (ERK1/2)通路，增强 B 细胞淋巴瘤-2 (Bcl-2，抗凋亡蛋白) 表达并抑制 Bcl-2 相关 X 蛋白(Bax，促凋亡蛋白)活性，从而保护心肌细胞免受脓毒症损伤[17] [18]；

③ 抑制 Toll 样受体 4/髓样分化因子 88/核因子 κB (TLR4/MyD88/NF-κB)通路，减轻急性肾损伤(AKI)

中的炎症反应和氧化应激[19] [20]；

同时，该药物还能减少中性粒细胞胞外诱捕网(NETs)的形成。在肾缺血再灌注损伤(IRI)模型中，西维来司他钠可降低 NETs 相关标志物(如髓过氧化物酶 MPO、瓜氨酸化组蛋白 H3 CitH3)的水平，从而减轻肾小管损伤和细胞凋亡[19]。

2.2. 西维来司他钠治疗 ARDS 的临床证据

针对 ARDS，西维来司他钠在脓毒症或 COVID-19 相关 ARDS 患者中显著改善氧合功能，表现为提高氧合指数(PaO_2/FiO_2)并缩短机械通气时间[21]，同时降低 28 天死亡率(风险比 HR = 0.32) [14]，尤其在基线氧合指数 < 200 mmHg 的亚组中，死亡风险显著降低 86% [22]。此外，该药物还能减轻肺损伤，具体表现为降低肺湿/干重比(W/D)、炎症因子(IL-8, TNF-α)及 NE 水平[16]。

西维来司他钠可提供多器官保护：

① 心脏保护：改善脓毒症心肌功能障碍(SIMD)，提升左心室收缩压(LVSP)及心功能指标，并减少心肌细胞凋亡[17]。

② 肾脏保护：降低急性肾损伤患者的血清肌酐、尿素氮及肾损伤分子(KIM-1)，同时抑制氧化应激[19] [23]。

③ 胃肠道保护：减轻脓毒症患者胃肠功能障碍(GIDS 评分)，降低喂养不耐受(FI)发生率[24]。

在心血管手术(尤其是接受体外循环的患者)中，西维来司他钠的应用可减少术后肺损伤，具体表现为降低急性肺损伤/急性呼吸窘迫综合征(ALI/ARDS)发生率，抑制炎症反应(如白细胞计数 WBC 和降钙素原 PCT 水平下降) [21] [25]，并改善术后氧合指数，缩短机械通气时间[21])。

3. 俯卧位通气治疗 ARDS

3.1. 俯卧位通气治疗 ARDS 的作用机制

① 血流动力学优化：通过重新分布重力依赖区的血流分布，优化通气/血流(V/Q)匹配，减少肺内分流，从而改善 V/Q [26]-[28]。在 COVID-19 相关 ARDS (C-ARDS)患者中，该干扰尤其显著降低肺内分流分数和死腔容积[27]-[29]。

② 促进肺复张：增加背侧肺泡复张，减轻腹侧肺泡过度扩张，优化肺应力分布[28] [30]。C-ARDS 研究证实该体位显著增加肺复张容积并减少萎陷伤[28]。

③ 优化通气分布：与仰卧位相比，该体位使肺组织应力分布更均匀，降低呼吸机相关性肺损伤(VILI)风险[31] [32]。

3.2. 俯卧位通气治疗 ARDS 的临床证据

在临床证据方面，俯卧位通气可显著改善重症 ARDS 患者的生存率，每日 12~16 小时的俯卧位通气可显著降低死亡率，已被指南推荐为标准治疗[31] [33] [34]。回顾性研究表明，严重 ARDS 患者死亡率 41%，其中俯卧位通气应用率达 61% [35]。在 C-ARDS 患者中，俯卧位通气可安全有效地改善氧功能，并被推荐作为机械通气患者的常规辅助治疗[28] [36]-[39]。

俯卧位通气可显著优化多项生理指标：① 77.8%~87.8%的患者氧合指数(PaO_2/FiO_2)显著提升[35] [38] [40]-[42]。② 心脏术后 ARDS 患者实施俯卧位通气后，其血氧指标显著优于仰卧位[43]。③ 改善呼吸力学，表现为降低呼吸阻力及平台压[27] [42]。值得注意的是，该干预在 ECMO 联合 Impella 支持的患者中下仍具备良好的安全性[44]。

在特殊人群中应用证据：① 儿童 ARDS：可改善氧合指数，但未显著缩短机械通气时长，需更多高

质量随机对照试验(RCT)验证[45]；② 妊娠合并 ARDS：作为辅助治疗安全有效，其适应证标准与其他患者一致[46]；③ 脓毒症相关 ARDS：显著改善氧合及呼吸功能，且安全性良好[47]。

4. 西维来司他钠联合俯卧位通气治疗 ARDS 的作用机制及临床证据

ARDS 的核心病理包括中性粒细胞介导的失控性炎症反应和通气－灌注失衡。西维来司他钠作为选择性中性粒细胞弹性蛋白酶(NE)抑制剂，通过特异性抑制 NE 活性减轻肺组织炎症反应(尤其在脓毒症或 COVID-19 诱因的 ARDS 中)，显著降低关键炎症因子(TNF-α, IL-8)水平及肺微血管通透性，从而减少中性粒细胞浸润和肺水肿形成[12] [48] [49]。俯卧位通气通过重力依赖机制优化通气分布，促进背侧肺泡复张，减少肺内分流和死腔分数，减轻剪切应力及气压伤风险[27]-[29]，同时间接抑制中性粒细胞募集及局部炎症因子积累[27] [32]。通过分别分析西维来司他钠和俯卧位通气的机制与临床证据，可以推断两者潜在的协同效应体现在三个层面：

① 炎症抑制互补：西维来司他钠从分子层面阻断 NE 介导的炎症级联(如抑制血管细胞黏附分子-1 (VCAM-1)和前列腺素内过氧化物合酶 2 (PTGS2)表达[48])，而俯卧位从物理层面减轻机械应力诱导的肺损伤，共同遏制炎症级联放大[28]。

② 氧合改善协同：西维来司他钠通过减轻肺水肿(表现为肺湿/干重比降低)改善氧合功能[14] [48] [50]；俯卧位则通过优化通气－灌注匹配提升 PaO_2/FiO_2 [27]-[29] [33] [46]，两者结合可加速氧合恢复并增强肺泡复张效率[33] [50]。

③ 并发症控制潜力：西维来司他钠缩短机械通气时间及 ICU 住院天数[14] [50]；俯卧位降低平台压和气压伤风险[26] [33] [51]。联合应用可能协同减少呼吸机相关肺炎(VAP)等并发症，缓解体位操作不适(如膈肌做功减少[32])，并缩短整体治疗周期。

综上所述，西维来司他钠靶向早期炎症损伤(如血管内皮损伤和细胞凋亡[12] [48])，而俯卧位通气解决中后期通气障碍(包括死腔减少和氧合提升[27] [28])，两者共同构建针对脓毒症或 COVID-19 相关 ARDS 的多层面保护网络。

既往文献，直接针对西维来司他钠联合俯卧位通气的研究较少，但提供了西维来司他钠和俯卧位通气的独立临床证据，同时有病例报告提示联合使用的可行性。例如：一项病例报告[52]表明，苯中毒诱发的 ARDS 患者联用俯卧位与西维来司他钠后，氧合功能快速改善且未发生不良事件。根据作用机制推断：两者干预措施独立改善氧合(西维来司他钠通过降低中性粒细胞弹性蛋白酶(NE)及血管细胞黏附分子-1 (VCAM-1)等炎症标志物水平[14] [48]，俯卧位通气通过优化通气灌注匹配[28] [29]，提示联合可能增强临床疗效，尤其针对炎症驱动型 ARDS 患者中。西维来司他钠联用其他抗炎药(如乌司他丁)已显示出协同效应趋势[53]，但其与俯卧位通气直接联合俯卧位的高质量研究仍待补充。

西维来司他钠(通过抑制 NE 介导的炎症级联反应)与俯卧位通气(通过优化通气分布)在 ARDS 治疗中具有互补协同潜力：前者改善氧合指数、缩短机械通气时间并降低死亡率[14] [22] [50]；后者则有效提升生存率及肺复张效率[29] [33] [51]。现有病例报告[52]初步支持该联合方案的安全性及可行性，未来需通过更多高质量研究验证其协同效应，从而优化重症 ARDS 的个体化治疗策略

5. 联合治疗方案的关键挑战及未来展望

既往研究中仅存在少量间接证据支持西维来司他钠联合俯卧位通气治疗急性 ARDS 的方案，例如一项病例报告描述了两种干预措施的同时应用[52]。当前联合治疗方案面临的核心挑战包括：

① 机制协同性证据不足：西维来司他钠主要靶向炎症级联反应(如抑制中性粒细胞弹性蛋白酶活性) [12] [54]，而俯卧位通气则通过优化通气－灌注匹配改善氧合[26] [55]。尽管理论推测两者机制互补，但

缺乏直接研究评估其协同效应或潜在拮抗作用，可能导致疗效未最大化或叠加不良反应(如血流动力学波动) [48] [54]。

② 高质量临床证据缺失：既往研究缺乏直接比较联合治疗与单一干预的随机对照试验(RCT)，导致联合方案的相对效益与风险难以量化。例如，西维来司他钠的死亡率获益仅在特定人群(如脓毒症相关ARDS)中被证实[14] [56]，而俯卧位通气的生存率改善高度依赖于早期实施(确诊后 12~24 小时内) [30] [55]。联合治疗的时机选择(如药物启动与通气时序匹配)及剂量优化尚无循证依据。

一项病例报告初步证实了联合应用的可行性及安全性[52]，未来亟需设计严谨的 RCT 研究评估其协同增效潜力，例如，建议开展一项针对特定 ARDS 亚型(如脓毒症相关、高炎症表型)的多中心、随机、安慰剂对照试验，明确提出主要研究终点(如 28 天无呼吸机天数)、次要终点(如氧合指数、炎症因子水平)以及样本量估算的基本考量，通过此类研究，不仅能明确联合治疗的绝对效益，还可通过亚组分析识别最佳获益人群，最终为个体化治疗提供高级别证据支持。

6. 总结

综上所述，西维来司他钠联合俯卧位治疗 ARDS 当前面临的主要挑战是疗效不一致、机制整合缺失和临床证据不足。未来将侧重于机制研究、患者分层和联合方案优化，以期提升疗效并降低风险，由于文献缺乏直接讨论联合治疗的数据，未来需要更多针对性研究验证其实际价值。

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