

· 论著 ·

## 肺移植术后持续雾化治疗对肺功能及相关并发症的影响

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**【摘要】** **目的** 探讨肺移植术后持续雾化治疗对肺移植受者肺功能及相关并发症的影响。**方法** 回顾性分析郑州大学第一附属医院肺移植外科在2013年6月至2024年12月行同种异体肺移植的71例受者的一般资料。根据受者出院后是否持续接受雾化治疗3个月以上分为观察组（持续雾化治疗）和对照组（自行终止雾化治疗）。主要观察指标为受者术后6个月时的肺功能指标，包括第1秒用力呼气容积占预计值百分比（FEV<sub>1</sub>% pred）、用力肺活量占预计值百分比（FVC% pred）、第1秒用力呼气容积与用力肺活量比值占预计值百分比（FEV<sub>1</sub>/FVC% pred）、25%用力肺活量时的用力呼气流量占预计值百分比、50%用力肺活量时的用力呼气流量占预计值百分比、75%用力肺活量时的用力呼气流量占预计值百分比、经单次呼吸法测定的校正后一氧化碳弥散量占预计值百分比、校正后一氧化碳弥散量与肺泡容积比值占预计值百分比，同时分析受者术后肺部感染年发生率、生存率及严重气道并发症未发生率。**结果** 肺移植术后6个月时，观察组受者的FEV<sub>1</sub>% pred、FVC% pred均优于对照组受者[FEV<sub>1</sub>% pred为76%（60%，91%）比67%（62%，78%），FVC% pred为（75±13）%比（69±11）%，均为P<0.05]。观察组的肺部感染年均发生率低于对照组（P=0.023），其发生风险为对照组的0.485倍。两组间的中位生存时间和严重气道并发症未发生率差异均无统计学意义（均为P>0.05）。**结论** 肺移植术后持续雾化治疗能有效改善受者的肺功能，降低肺部感染的年发生率，对肺功能的长期维护具有积极作用。

**【关键词】** 肺移植；雾化治疗；肺功能；肺部感染；严重气道并发症；慢性移植肺功能障碍；闭塞性细支气管炎综合征；体质指数

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### The impact of continuous nebulization therapy on pulmonary function and related complications after lung transplantation

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**【Abstract】** **Objective** To investigate the impact of continuous nebulization therapy after lung transplantation on pulmonary function and related complications in lung transplant recipients. **Methods** A retrospective analysis was conducted on the general data of 71 recipients who underwent allogeneic lung transplantation at the Department of Thoracic Surgery, the First Affiliated Hospital of Zhengzhou University, from June 2013 to December 2024. Recipients were divided into observation group (those who continued nebulization therapy for more than 3 months after discharge) and control group (those who discontinued nebulization therapy on their own). The main observation indicators were pulmonary function indicators at 6 months after surgery, including forced expiratory volume in the first second as a percentage of predicted value (FEV<sub>1</sub>% pred), forced vital capacity as a percentage of predicted value (FVC% pred), ratio of

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forced expiratory volume in the first second to forced vital capacity as a percentage of predicted value ( $FEV_1/FVC\%$  pred), forced expiratory flow at 25%, 50% and 75% of forced vital capacity as a percentage of predicted value, and the percentage of predicted value of corrected carbon monoxide diffusion capacity measured by single-breath method, as well as the ratio of corrected carbon monoxide diffusion capacity to alveolar volume as a percentage of predicted value. Additionally, the annual incidence of postoperative pulmonary infections, survival rate and the rate of no severe airway complications were analyzed. **Results** At 6 months after lung transplantation, the  $FEV_1\%$  pred and  $FVC\%$  pred of the observation group were better than those of the control group [ $FEV_1\%$  pred was 76% (60%, 91%) vs. 67% (62%, 78%),  $FVC\%$  pred was  $(75 \pm 13)\%$  vs.  $(69 \pm 11)\%$ , both  $P < 0.05$ ]. The observation group had a lower annual incidence of pulmonary infections compared to the control group ( $P = 0.023$ ), with a risk of 0.485 times that of the control group. There were no statistically significant differences between the two groups in median survival time and the rate of no severe airway complications (both  $P > 0.05$ ). **Conclusions** Continuous nebulization therapy after lung transplantation may effectively improve pulmonary function, reduce the annual incidence of pulmonary infections, and play a positive role in the long-term maintenance of pulmonary function.

**【Key words】** Lung transplantation; Nebulization therapy; Pulmonary function; Pulmonary infection; Severe airway complication; Chronic lung allograft dysfunction; Bronchiolitis obliterans syndrome; Body mass index

肺移植是终末期肺病患者延长生命、改善生活质量的有效治疗手段<sup>[1]</sup>。随着手术技术的进步和免疫抑制方案的优化,肺移植受者的围手术期生存率显著提高。然而,术后并发症特别是慢性移植肺功能障碍(chronic lung allograft dysfunction, CLAD),仍是制约受者长期预后的主要障碍<sup>[2]</sup>。CLAD以进行性、不可逆的肺功能下降为特征,其主要临床表型包括闭塞性细支气管炎综合征(bronchiolitis obliterans syndrome, BOS)和限制性移植物综合征<sup>[3-4]</sup>。BOS是CLAD中最常见的表型,也是导致肺移植受者远期死亡的首要原因<sup>[5]</sup>。CLAD的发生机制复杂,涉及慢性排斥反应、反复感染、胃食管反流及气道并发症等多种免疫和非免疫因素,这些因素诱导气道和肺实质的慢性炎症与纤维化,进而导致肺功能不可逆损害<sup>[6-7]</sup>。鉴于CLAD的复杂病理机制,靶向气道和肺实质保护的新型干预策略亟待开发与应用。

肺移植术后受者的气道面临独特的挑战,由于神经支配缺失和局部免疫功能改变,受者常出现咳嗽反射减弱、纤毛功能受损及痰液黏稠等问题,导致分泌物滞留<sup>[8]</sup>。这不仅直接影响通气功能,还显著增加呼吸道感染风险,而反复感染是诱发和加速CLAD进展的关键因素<sup>[2]</sup>。因此,有效的气道管理和长期肺功能维护对肺移植受者的长期生存至关重要。

雾化治疗因其可将药物以气溶胶形式精准递送至气道和肺部而具有显著优势,在减少全身不良反应的同时,发挥气道湿化、局部抗炎、抗菌、黏液溶解及支气管扩张等作用<sup>[9]</sup>。目前,肺移植术后常用的雾化

药物包括抗生素(如妥布霉素、阿米卡星、两性霉素B及阿奇霉素)、皮质类固醇(如布地奈德)、支气管扩张剂(如沙丁胺醇)及黏液溶解剂(如乙酰半胱氨酸、高渗盐水)。这些药物通过有效控制气道局部感染、减轻炎症反应和清除黏液栓,可减少继发性肺损伤,从而可能延缓CLAD的启动与进展进程,并最终有益于肺功能维护及整体预后<sup>[10-11]</sup>。

基于上述机制与潜在临床价值,本研究通过回顾性分析郑州大学第一附属医院肺移植外科接受肺移植术患者的临床数据,以术后6个月肺功能作为主要观察终点,探索持续雾化治疗对肺功能改善的长期影响,填补当前雾化策略在移植物维护中的证据空白。同时,鉴于雾化治疗在控制感染与减轻炎症方面的潜在作用及其与CLAD病理和预后的关联性,研究进一步分析其对肺部感染年发生率和严重气道并发症等次要终点的影响,旨在为优化肺移植术后气道管理策略提供更有力的证据。

## 1 资料与方法

### 1.1 一般资料

回顾性分析郑州大学第一附属医院肺移植外科在2013年6月至2024年12月行同种异体肺移植的受者资料,包括性别、年龄、体质量指数(body mass index, BMI)、术前吸烟史、术前诊断以及移植手术类型等。纳入标准包括:(1)术后生存时间 $\geq 6$ 个月;(2)接受移植时年龄 $\geq 18$ 岁。排除标准包括:(1)心肺联合移植及接受二次移植受者;

(2) 临床资料不完整的受者; (3) 随访中断的受者。研究最终纳入受者共 71 例, 所有受者均接受标准化肺移植术后管理, 包括抗感染、营养支持和康复训练, 并定期接受胸部 CT、支气管镜及肺功能检查。本研究获得郑州大学第一附属医院医学伦理委员会批准 (2025-KY-0954), 所有受者及家属均签署知情同意书。

### 1.2 研究分组

所有受者在术后住院期间常规接受雾化吸入治疗, 用药方案包括: 盐酸氨溴索+丙酸倍氯米松或乙酰半胱氨酸+布地奈德或单纯使用生理盐水。出院时建议所有受者院外继续原有方案接受雾化治疗, 部分受者持续雾化治疗 3 个月以上, 分为观察组 (35 例); 其余受者出院后在 3 个月内自行终止雾化治疗, 分为对照组 (36 例)。

### 1.3 免疫抑制方案

所有受者在移植过程中接受甲泼尼龙 500 mg 静脉注射, 术后维持阶段均为他克莫司或环孢素+吗替麦考酚酯+糖皮质激素三联免疫抑制方案。

### 1.4 观察指标

主要观察指标为术后 6 个月时复查的肺功能指标, 包括第 1 秒用力呼气容积占预计值百分比 ( $FEV_1\% \text{ pred}$ )、用力肺活量占预计值百分比 ( $FVC\% \text{ pred}$ )、第 1 秒用力呼气容积与用力肺活量比值占预计值百分比 ( $FEV_1/FVC\% \text{ pred}$ )、25% 用力肺活量时的用力呼气流量占预计值百分比 ( $FEF_{25}\% \text{ pred}$ )、50% 用力肺活量时的用力呼气流量占预计值百分比 ( $FEF_{50}\% \text{ pred}$ )、75% 用力肺活量时的用力呼气流量占预计值百分比 ( $FEF_{75}\% \text{ pred}$ )、经单次呼吸法测定的校正后肺一氧化碳弥散量占预计值百分比 ( $D_LCOc \text{ SB}\% \text{ pred}$ )、校正后肺一氧化碳弥散量与肺泡容积比值占预计值百分比 ( $D_LCOc/VA\% \text{ pred}$ )。次要观察指标包括术后生存时间、术后肺部感染年发生率、术后首次发生严重气道并发症时间。

### 1.5 统计学方法

采用 SPSS 27.0.1 统计学软件进行分析。计数资料以率表示, 无序分类资料组间比较采用  $\chi^2$  检验或 Fisher 精确检验, 有序分类资料比较采用 Mann-Whitney 秩和检验。计量资料以均数±标准差或中位数 (下四分位数, 上四分位数) 表示, 两组间比较采用独立样本  $t$  检验或 Mann-Whitney 秩和检验。术后

感染发生率采用负二项回归模型分析, 生存分析使用 Kaplan-Meier 曲线和 log-rank 检验。以双侧  $P < 0.05$  为差异有统计学意义。

## 2 结果

### 2.1 一般资料

对比两组受者一般资料, 包括性别、年龄、BMI、吸烟史、移植类型以及原发病, 两组受者间差异均无统计学意义 (均为  $P > 0.05$ , 表 1)。

表 1 两组受者一般资料比较

Table 1 Comparison of general information of recipients between two groups

指标	观察组 (n=35)	对照组 (n=36)	P值
性别[n (%)]			0.284
男	29 (83)	26 (72)	
女	6 (17)	10 (28)	
年龄 ( $\bar{x} \pm s$ , 岁)	54 ± 13	52 ± 14	0.687
BMI ( $\bar{x} \pm s$ , kg/m <sup>2</sup> )	22 ± 3	21 ± 3	0.607
吸烟史[n (%)]			0.638
无	17 (49)	20 (56)	
有	18 (51)	16 (44)	
移植类型[n (%)]			0.909
双肺移植	18 (51)	19 (53)	
单肺移植	17 (49)	17 (47)	
原发病[n (%)]			0.142
限制性肺病 <sup>①</sup>	26 (74)	19 (53)	
阻塞性疾病 <sup>②</sup>	1 (3)	4 (11)	
其他肺病 <sup>③</sup>	8 (23)	13 (36)	

注: ①限制性肺病包括特发性肺纤维化、继发性肺纤维化、继发性间质性肺炎、免疫相关性间质性肺病等; ②阻塞性疾病包括慢性阻塞性肺疾病、支气管哮喘、肺气肿等; ③其他肺病包括肺尘埃沉着病、支气管扩张、肺泡蛋白沉积症、BOS、百草枯相关纤维化、肺动脉高压等。

### 2.2 移植术后肺功能比较

对两组肺移植受者术后 6 个月的肺功能指标进行比较, 结果显示, 观察组受者肺功能指标中  $FEV_1\% \text{ pred}$ 、 $FVC\% \text{ pred}$  均优于对照组受者 (均为  $P < 0.05$ , 表 2), 其余肺功能指标差异均无统计学意义 (均为  $P > 0.05$ )。

表 2 两组受者术后肺功能比较

Table 2 Comparison of postoperative pulmonary function of recipients between two groups

指标	观察组 (n=35)	对照组 (n=36)	P值
FEV <sub>1</sub> % pred[M (P <sub>25</sub> , P <sub>75</sub> ), %]	76 (60, 91)	67 (62, 78)	0.046
FVC% pred (x̄±s, %)	75 ± 13	69 ± 11	0.048
FEV <sub>1</sub> /FVC% pred[M (P <sub>25</sub> , P <sub>75</sub> ), %]	105 (97, 112)	100 (86, 110)	0.080
FEF25% pred[M (P <sub>25</sub> , P <sub>75</sub> ), %]	74 (60, 86)	77 (69, 88)	0.448
FEF50% pred[M (P <sub>25</sub> , P <sub>75</sub> ), %]	70 (56, 81)	70 (55, 80)	0.881
FEF75% pred[M (P <sub>25</sub> , P <sub>75</sub> ), %]	70 (49, 104)	75 (47, 93)	0.791
D <sub>L</sub> COc SB% pred (x̄±s, %)	60 ± 19	53 ± 18	0.119
D <sub>L</sub> COc/VA% pred (x̄±s, %)	86 ± 25	80 ± 19	0.297

2.3 肺部感染年均发生率

使用生存时间(年)的自然对数作为偏移量构建术后肺部感染发生率的负二项回归模型,过离散检验支持模型适用性(O值=3.418, P<0.05)。结果显示,观察组感染年均发生率低于对照组(回归系数=-0.724, P=0.023),其发生风险为对照组的0.485倍[95%可信区间(confidence interval, CI)0.259~0.906]。对照组受者的基础感染发生率为1.978次/年(95%CI 1.337~2.619)。模型似然比检验证实组别变量对感染次数具有显著解释作用(P=0.023)。本研究绘制的小提琴图直观地展示了观察组与对照组受者在术后年均感染次数的分布情况,由图1可见,观察组的数据整体分布位置比对照组低[0.90(0.40, 1.50)比1.35(0.95, 2.25)],这与负二项回归模型得出观察组感染年均发生率低于对照组的结果相吻合。

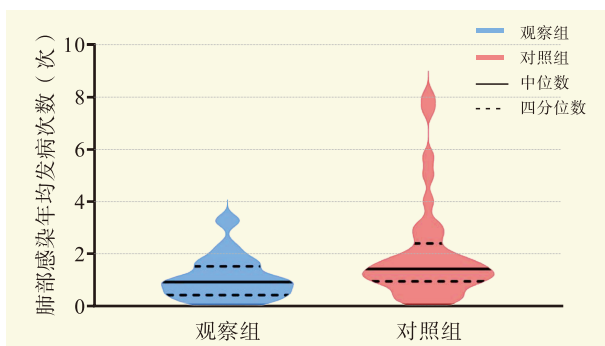


图 1 两组受者术后肺部感染年均发病次数比较  
Figure 1 Comparison of average annual number of cases of postoperative pulmonary infections of recipients between two groups

2.4 生存率分析

通过Kaplan-Meier生存曲线评估两组受者术后总生存期差异,log-rank检验进行生存分析。其中观察组中位生存时间为2.100年(95%CI 2.055~3.043),对照组为2.150年(95%CI 2.086~3.081)。Cox比例风险模型计算风险比为0.974(95%CI 0.458~2.073)。两组受者生存率差异无统计学意义(P>0.05,图2)。

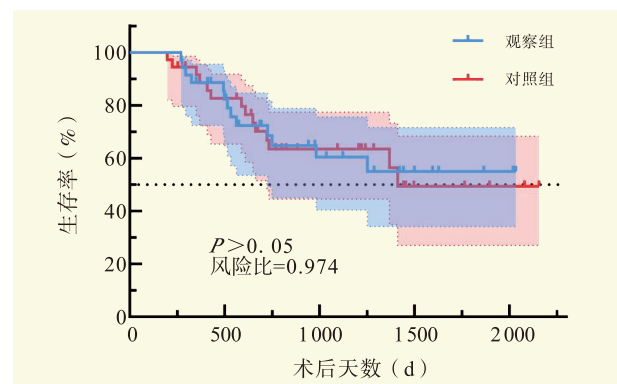


图 2 两组受者术后生存率比较

Figure 2 Comparison of postoperative survival rates of recipients between two groups

2.5 气道并发症未发生率分析

采用Kaplan-Meier法评估两组气道并发症发生风险,采用log-rank检验进行组间比较。在研究的观察期内,观察组和对照组超过50%研究受者均未出现严重气道并发症,因此无法确定事件发生中位数。Cox比例风险模型计算风险比为0.674(95%CI 0.281~1.621)。两组受者气道并发症未发生率差异无统计学意义(P>0.05,图3)。

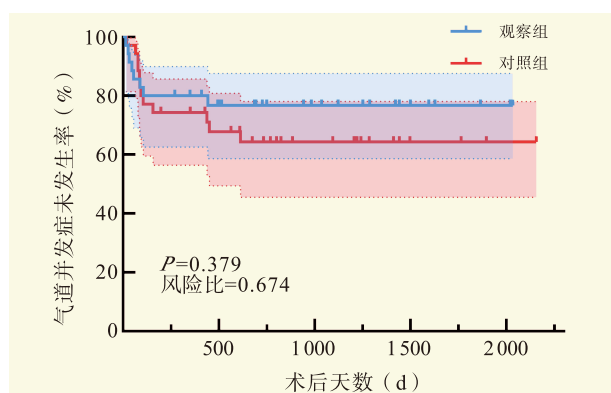


图3 两组受者术后严重气道并发症未发生率比较

Figure 3 Comparison of non-occurrence rate of severe airway complications after surgery of recipients between two groups

### 3 讨论

肺功能是评估肺部疾病及肺移植术后诊断 CLAD 的重要标准<sup>[12]</sup>。本研究回顾性分析 71 例肺移植受者,探讨持续雾化治疗对术后肺功能、感染控制及临床结局的影响。结果显示,观察组术后 6 个月 FEV<sub>1</sub>% pred 与 FVC% pred 均优于对照组(均为  $P < 0.05$ ),肺部感染年均发生率降低。然而,两组间中位生存时间、生存曲线以及严重气道并发症未发生率差异均无统计学意义。

肺功能检查中,FEV<sub>1</sub>% pred 是代表指标,与 FVC% pred、FEV<sub>1</sub>/FVC% pred 在诊断 CLAD 方面有重要作用<sup>[13]</sup>。肺一氧化碳弥散量(diffusing capacity of the lungs for carbon monoxide, D<sub>L</sub>CO)直接反映肺泡-毛细血管膜气体交换效率,对早期肺纤维化等病变敏感<sup>[11]</sup>。用力呼气流量(forced expiratory flow, FEF)特异性反映小气道通畅性,是气道阻塞性病变的早期预测因子<sup>[14-15]</sup>。综合多参数可早期识别 CLAD,尤其是 BOS,并精准评估干预措施疗效。本研究选择术后 6 个月为评估时间窗,此时移植肺已度过急性期,且 CLAD 尚未高发。Verleden 等<sup>[2]</sup>与蔡宇航等<sup>[7]</sup>研究显示,术后 6 个月肺功能趋于稳定,FEV<sub>1</sub> 接近峰值,是评估干预效果的黄金期。

支气管扩张剂或高渗盐水治疗后 D<sub>L</sub>CO 的改善<sup>[16-17]</sup>,表明其效应源于间接机制,通过改善气流和清除阻塞<sup>[18]</sup>,增加功能性肺泡的数量,扩大气体交换面积,同时抗炎作用也可减轻间质水肿和改善膜效率。FEF(尤其是 FEF 25%~75%)对小气道变化的敏感性高于 FEV<sub>1</sub><sup>[19-20]</sup>。在本研究中,两组 D<sub>L</sub>CO 及

FEF 均无显著差异,可能归因于移植受者病肺限制、随访期不足和 FEF 个体变异性等。后续将通过分层分析(移植类型或术后时间)结合影像学评估深化探索。

肺移植受者需终身服用免疫抑制药以预防排斥反应,但这会增加肺部感染和 CLAD 的发生风险,导致肺功能进行性下降<sup>[21]</sup>。雾化疗法将药物直接输送至气道,规避肝脏首过效应,在实现肺部药物高浓度的同时减少全身吸收,减少体质量增加、血糖升高、骨质疏松等全身性不良反应风险<sup>[22-25]</sup>。De Soyza 等<sup>[26]</sup>研究表明每日 2 次吸入 800 μg 布地奈德在肺移植受者中可以有效控制淋巴细胞性支气管炎的发生。此外,雾化生理盐水及黏液溶解剂通过稀释黏稠痰液、增强纤毛清除功能及刺激有效咳嗽,对抗移植肺因去神经支配导致的黏膜清除障碍,减少分泌物滞留与感染风险,其中高渗盐水雾化被证实可改善肺功能并降低感染频率<sup>[27-29]</sup>。雾化抗生素同样可有效预防感染,70% 的欧洲肺移植中心建议吸入抗生素 2~4 个月以预防肺部感染<sup>[30]</sup>,但需要持续病原学监测,可能降低受者依从性。值得注意的是,支气管扩张剂因肺移植后急性去神经支配导致支气管反应性显著降低,临床获益有限,故本研究未采用<sup>[31]</sup>。

本研究证实持续雾化显著降低肺移植受者术后肺部感染率。首先,感染反复发作可通过持续性同种异体炎症反应及病原体直接作用加速 BOS 的气道重塑进程<sup>[32]</sup>;其次,感染相关急性肺损伤会破坏肺泡-毛细血管膜,损害 D<sub>L</sub>CO 并降低移植物功能基线水平<sup>[33]</sup>。雾化治疗通过双重机制阻断上述恶性循环:(1)黏液溶解剂增强黏膜纤毛清除效能<sup>[17,29]</sup>,减少分泌物滞留及病原体定植风险<sup>[34]</sup>;(2)吸入性糖皮质激素抑制局部炎症反应和减少排斥反应风险<sup>[26]</sup>。这种干预不仅避免急性感染期肺功能波动,更通过延缓 CLAD 进展为中远期肺功能的稳定提供根本保障<sup>[32]</sup>。

本研究未发现两组在生存时间或严重气道并发症发生率上差异存在统计学意义。回顾性设计制约了移植前基线数据(如呼出气一氧化氮)的完整性,影响术后肺功能及气道炎症的动态评估;同时未纳入血气、B 型利钠肽等多维指标,难以全面分析。本研究的样本量相对较少,可能不足以在有限的随访时间内充分显示对长期生存率和发生率较低的严重气道并发症的显著影响。

肺移植受者的长期生存受多种因素影响, 如供肺质量、受者依从性等<sup>[35]</sup>, 回顾性研究难以完全控制这些变量。吸入性皮质类固醇主要针对嗜酸性粒细胞或淋巴细胞相关炎症, 对 CLAD 不可逆的纤维化重塑无效<sup>[36-37]</sup>。因此, 常规雾化治疗既无法改变 CLAD 的纤维化进程, 也无法纠正气道结构性异常, 对改善长期生存率或预防严重并发症的效果有限<sup>[38-39]</sup>。

综上, 肺移植术后持续雾化治疗能有效改善肺移植受者的肺功能并控制感染, 对肺功能的长期维护具有积极作用, 但并不能改善生存或减少严重气道并发症。

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