·专家论坛·

# 基于“肺朝百脉”理论探讨肺血管病变在慢性阻塞性肺疾病中的作用及意义

李康沉 田燕歌 张蓝熙 朱丽华 李敏艳

河南中医药大学，呼吸疾病中医药防治省部共建协同创新中心/河南省中医药防治呼吸病重点实验室，河南 郑州 450046

通信作者：田燕歌，Email：yange0910@126.com

【摘要】 中医认为“肺朝百脉，主治节”，肺血管即是“百脉”的终末和起始处。肺朝百脉不利导致的肺血管异常是慢性阻塞性肺疾病（COPD）发生发展中重要的病理改变，包括肺血管炎症、肺血管内皮功能障碍和肺血管重塑等。本文基于“肺朝百脉”理论阐述COPD肺血管改变的意义，并探讨中医药对COPD的治疗作用，为COPD提供新的治疗观念。

【关键词】 慢性阻塞性肺疾病； 肺朝百脉； 肺血管

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**Discussion on effect and significance of pathological changes in pulmonary vessels in chronic obstructive pulmonary disease based on "all blood vessels meet in the lung" theory** *Li Kangchen, Tian Yange, Zhang Lanxi, Zhu Lihua, Li Minyan*

*Co-construction Collaborative Innovation Center for Chinese Medicine and Respiratory Diseases by Henan & Education Ministry of P.R. China/Henan Key Laboratory of Chinese Medicine for Respiratory Disease, Henan University of Chinese Medicine, Zhengzhou 450046, Henan, China*

*Corresponding author: Tian Yange, Email: yange0910@126.com*

【Abstract】 The theory of traditional Chinese medicine (TCM) suggests "all blood vessels meet in the lung". According to this theory, pulmonary vessel is both start and end point of all vessels. The pulmonary vascular abnormalities caused by "all vessels converging in lung" malfunction are important pathological changes in the occurrence and development of chronic obstructive pulmonary disease (COPD), including pulmonary vascular inflammation, pulmonary vascular endothelial dysfunction and pulmonary vascular remodeling. Based on the theory of "all blood vessels meet in the lung", this paper reviews the significance of pulmonary vascular dysfunction in COPD, and explores the therapeutic effect of TCM on it, which provides a new therapeutic method for COPD.

【Key words】 Chronic obstructive pulmonary disease; All blood vessels meet in the lung; Pulmonary vessels

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慢性阻塞性肺疾病（COPD）严重危害公众健康，已成为我国三大最常见的慢性疾病之一[1-2]。尽管支气管和肺泡结构异常是COPD的主要病理改变，但近年来，肺血管病变也逐渐受到重视，在轻度COPD患者及无症状的吸烟者中即出现肺微血管血流量的显著异常，且随病情逐渐加重，在临床已确诊的COPD患者中，30%～70%患者存在显著的肺血管疾病[3-6]。肺血管结构改变及功能异常影响气体交换，一旦出现肺动脉高压（PH），患者肺动脉血流动力学、右心功能及运动耐力已发生改变[7]，是COPD患者病情恶化和生存率降低的主要原因[8-9]。中医认为“肺朝百脉，主治节”，肺血管即是“百脉”的终末和起始处，在调节机体气血津液循行中起重要作用。本文基于“肺朝百脉”理论对COPD肺血管的病理生理改变及治疗靶点进行综述。

## 1 “肺朝百脉”的生理及病理意义

“肺朝百脉”首见于《素问·经脉别论》：“脉气流经，经气归于肺，肺朝百脉，输精于皮毛”，即全身血液，经百脉聚于肺，并通过肺的呼吸运动进行气体交换，最后输送至全身。生理上，“肺朝百脉”体现了肺与脉、肺与血、肺与心的相互关系[10]。肺主气，心主血，全身之血脉统属于心，虽然心脏的搏动是血液循行的基本动力，但血液能够正常运行于脉管之中，还需依赖肺气的推动与调节，即“肺朝百脉”功能由肺主气作用间接实现[11]；病理上，若外邪犯肺，可致肺朝百脉不利，肺失宣降，气上逆而作咳喘，气不布津而生痰浊，血行障碍而成淤滞。若肺气虚弱，宗气不足，气机不调，肺朝百脉不利，则不能助心行血而致百脉淤滞，表现为舌质紫暗、口唇发绀、胸中憋闷、气短气急等症状。总之，无论肺病

之虚实，皆可致肺朝百脉不利而成淤。Polosa等[12]研究发现，COPD加重期间凝血状态升高，这与中医外邪犯肺或肺气虚致肺朝百脉不利、血行不畅相一致。

## 2 COPD对肺血管变化的影响

**2.1** 肺血管病变促进COPD的发生发展：肺血管在COPD早期出现管壁增厚、内皮功能障碍，逐渐出现血管平滑肌增生；晚期有胶原沉积和毛细血管床破坏[13]。低氧性血管收缩和肺血管被动受压是肺血管病变的主要机制，其主要因素为肺血管炎症、肺血管内皮功能障碍和肺血管重塑等。

**2.1.1** 肺血管炎症：COPD长期反复发作及支气管周围炎和间质炎症，常累及临近肺小动脉，引起肺血管炎症。炎症细胞（$CD8^+$ T细胞亚群为主）通过释放细胞因子〔如白细胞介素-8（IL-8）〕和生长因子〔如血管内皮生长因子（VEGF）、转化生长因子β（TGF-β）〕等参与肺血管炎症[14]。炎症细胞和细胞因子的积累与Toll样受体-4（TLR4）的表达密切相关，TLR4在肺血管中过度表达，可诱导炎症细胞的不断浸润，改变肺血管通透性，促进基质金属蛋白酶和其他活性物质增加，进一步促进损伤修复过程[15]。慢性肺血管炎症引起的炎症损伤与修复过程使细胞外基质增加，平滑肌细胞肥大，肌型肺动脉肥厚狭窄，血管弹性降低，肺动脉压升高，心室重塑，最终导致PH和肺心病的发生。

**2.1.2** 肺血管内皮功能障碍：肺血管系统是肺内气体交换的关键，内皮细胞（EC）是覆盖在整个肺血管腔表面的异质性细胞单层[16]。肺血管EC具有多种功能，包括屏障功能、合成与分泌功能、调节新生血管生成和参与炎症反应等[17]。Polverino等[18]发现，EC功能障碍和损伤是导致COPD患者肺气肿和PH发生发展的关键过程。香烟烟雾（CS）作为COPD最主要的环境危险因素，通过抑制磷酸化黏着斑激酶（FAK）、RhoA GTP酶和组蛋白脱乙酰酶6等活化增加肺微血管单层EC通透性，破坏与维持细胞旁通透性有关的结构，最终引起肺血管EC屏障功能障碍[19-21]。肺血管内皮屏障功能受损、通透性增加，可使该区域组织水肿，导致支气管上皮通透性增加，炎症介质进入气道，增加气道阻力，促使COPD患者病情恶化。除屏障功能外，肺血管EC还可合成分泌多种血管活性物质和细胞因子，通过自分泌或旁分泌方式作用于效应细胞，调节血管功能。COPD患者早期由于各种因素的刺激使一氧化氮（NO）产生减少，内皮素-1（ET-1）、VEGF表达增高，引起肺微血管EC损伤和凋亡[22-24]。肺血管内皮受损可导致血管舒张功能降低、血液凝固性增加和血小板活化增强，增加COPD患者出现PH和形成血栓的风险[25]。总之，内皮功能障碍降低了血管内皮对炎症、凝血和血管张力的保护作用，增加COPD患者合并心血管疾病的风险。

**2.1.3** 肺血管重塑：肺血管重塑是COPD合并PH的主要特征，包括内膜增生、弹性蛋白和胶原沉积、肺小动脉肌化等[26]。血管壁的3层均参与了血管重塑过程，表现为内膜EC功能受损通透性增加、中膜肺动脉平滑肌细胞异常增殖、外膜细胞外基质（ECM）沉积和成纤维细胞活化[27]。外膜ECM的成熟在肺泡气体交换中起重要作用，ECM的主要成分是胶原，其成熟的关键过程是胶原蛋白与弹性蛋白的交联，ECM沉积是肺血管重塑的基础[28]。研究表明，低氧条件下，缺氧诱导因子-1α（HIF-1α）激活TGF-β1/Smad信号途径，促进胶原沉积[29]。COPD大鼠肺组织中胶原的合成与降解失衡，Ⅰ型、Ⅲ型、Ⅳ型胶原表达增多，有害物质聚集，导致肺顺应性降低、肺血管管腔狭窄和管壁增厚，引起肺血管重塑[30]。COPD患者肺血管重塑促使PH的发生发展，最终导致心室重构。

**2.2** 改善肺血管异常可能是治疗COPD的靶点：肺血管病变参与COPD的发生发展，改善肺血管异常可能是治疗COPD的重要靶点[31]。目前已有研究从肺血管炎症、内皮功能、血管重塑及其相关因子着手治疗COPD并取得了较大进展。

Yin等[32]研究发现，过氧化物酶体增殖物激活受体γ（PPAR-γ）激动剂罗格列酮可通过PPAR-γ依赖机制抑制TLR4的表达，降低IL-8、白三烯B4（LTB4）的释放，减轻肺血管炎症。NO是一种有效的可选择性肺血管扩张剂，对于血管内皮功能恢复有重要作用。Hajian等[33]通过功能性呼吸成像技术量化COPD患者短期脉冲式吸入NO后肺血管口径变化，发现大部分血管明显舒张，患者呼吸困难有所改善。沉默信息调节因子2相关酶1（SIRT1）是一种烟酰胺腺嘌呤二核苷酸（$NAD^+$）依赖性脱乙酰酶，可与NO生成系统相互作用，从而调节血管衰老和内皮功能障碍[34]；Arunachalam等[35]研究发现，用白藜芦醇预处理人脐静脉内皮细胞（HUVEC）可激活SIRT1，减轻CS对HUVEC的氧化应激损伤，使内皮型一氧化氮合酶（eNOS）乙酰化降低，进而维持或改善EC功能。VEGF和碱性成纤维细胞生长因子（FGF-2）在缺氧或CS刺激下释放并

参与血管重塑和气道炎症。Laddha等[36]通过总结VEGF和FGF-2在呼吸疾病中的分子机制，提出新的药物研究应集中在VEGF和FGF-2抑制剂方面；Wang等[37]研究发现，可溶性环氧化物水解酶抑制剂可显著降低COPD大鼠肺部VEGF水平，从而改善CS诱导的COPD；Yang等[38]用前臂静脉阻塞体积描记法评估COPD患者血管功能，发现口服可溶性环氧化物水解酶抑制剂可缓解血管内皮功能障碍。总之，改善肺血管异常可能是改善COPD症状及预后的潜在靶点。

## 3 基于“肺朝百脉”理论探讨中医药治疗COPD的思考

COPD起病于肺，“肺朝百脉”，肺气虚则无力行血脉，布津液，逐渐累及脾肾，即“肺不伤不咳，脾不伤不久咳，肾不伤不咳喘”。依据中医“整体观念”思想，脾肺相生，若脾气虚弱，运化功能减退，则水湿停聚而成痰饮；若肾精不足或久病及肾，肾不纳气，肺失肃降，可出现久咳喘促、头晕眼花、腰膝酸软等症，故应采用培补摄纳、补肺益肾、健脾益气养肺等法[39]。李建生教授[40]对不同中医证候COPD患者的生存质量进行测量，研究显示血瘀证患者的生存质量评分最低，且血瘀始终贯穿于COPD发生发展中，故还应重视活血化瘀法对COPD的治疗作用。基于COPD“正虚积损”病机，李建生教授[41]拟定了补益肺肾兼顾脾，佐以祛痰活血的调补肺肾系列方药，如补肺益肾、补肺健脾、益气滋肾等，该系列方药均可降低COPD大鼠右心室肥大指数，改善心肌超微结构，降低心肌细胞中ET-1、TGF-β、VEGF等细胞因子的表达，从而改善右心室重构，以补肺健脾和补肺益肾方改善尤为显著[42]。采用系统药理学对补肺益肾方作用靶点进行预测，发现10个潜在靶点归于VEGF通路，实验显示，发现该方可明显抑制COPD模型大鼠的肺损伤评分、肺小血管壁厚度、肺泡直径的增加及胶原沉积，改善肺血管重构[43-44]。基于“治节重建”理念，李泽庚教授创制“芪白平肺胶囊”（组成：川芎、黄芪、生晒参、五味子等），旨在益气化痰祛瘀，改善血液高凝状态，减轻肺血管重构[45]。依据“肺病多瘀”特点，韩桂玲等[46]采用补肺活血方药（组成：赤芍、黄芪、全瓜蒌、丹参等）抑制炎症反应，降低血液黏稠度，提高COPD患者治疗效果。

COPD主要病机为肺朝百脉不利、肺失治节。结合“肺朝百脉”理论和现代医学研究，发现肺血管改变在COPD发生发展中起关键作用，虽然GOLD指南中已将肺血管异常导致的PH列为COPD的主要病理机制之一，但仍缺乏有效的治疗药物，中医药治疗虽然取得了一定进展，但其机制研究不够深入。因此，今后将从以下几点开展工作：① 基于“肺朝百脉”理论，深入探讨COPD肺血管改变机制；② 观察中医药在疾病发展不同时期对于肺血管或心肺功能的疗效；③ 结合生物学先进技术，筛选COPD合并肺血管改变相关基因蛋白；④ 探讨中医药治疗COPD肺血管异常的潜在机制，为推动其预防及治疗提供新的思路和理论依据。

**利益冲突** 所有作者均声明不存在利益冲突

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