

心房颤动合并慢性阻塞性肺疾病的研究进展

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[摘要] 慢性阻塞性肺疾病(COPD)是心房颤动(简称房颤)患者常见的并发症之一,二者具有多项共同易患因素。一方面,COPD通过多种病理生理机制促进房颤的发生、发展,是影响房颤患者预后的重要因素,可导致患者临床不良事件和心血管病死亡风险增加;另一方面,合并房颤同样影响COPD患者的治疗策略及预后。因此,房颤合并COPD使患者的治疗面临极大挑战。本文总结近年来国内外关于房颤合并COPD的相关研究成果,从流行病学特点、病理生理学机制、患者管理、转归及预后等方面进行综述,以期对房颤合并COPD患者的多学科综合管理和个体化治疗提供帮助。

[关键词] 心房颤动;慢性阻塞性肺疾病;研究进展

Research progress on atrial fibrillation complicated with chronic obstructive pulmonary disease

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[Abstract] Chronic obstructive pulmonary disease (COPD) is one of the most common comorbidities in patients with atrial fibrillation, and the both diseases share a series of common risk factors. COPD promotes the occurrence and development of atrial fibrillation by variety of pathophysiological mechanisms, is the important factor affecting the prognosis of patient with atrial fibrillation, and results in an elevation of clinical adverse and cardiovascular death events. Atrial fibrillation also affects the treatment strategy and prognosis of COPD patients. Treatment plan for patients with both atrial fibrillation and COPD faced huge challenging. The research findings of home and abroad related to atrial fibrillation complicated with COPD were summarized in present paper from the aspects of epidemiology, pathophysiology mechanism, patient management, outcome and prognosis, in order to provide help for the integrated multidisciplinary management and individualized treatment for these patients.

[Key words] atrial fibrillation; chronic obstructive pulmonary disease; research progress

心房颤动(房颤)是常见的心律失常之一,影响了全球约3350万人口^[1]。房颤患者常存在多种并发症,这些并发症可增加房颤相关的住院风险和死亡风险^[2-3]。慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)是最常见的慢性呼吸系统疾病,也是心血管疾病主要的致死原因之一^[4]。越来越多的证据表明,COPD与房颤密切相关^[5-7]。COPD可促进房颤的发生和进展,进而影响房颤患者的生活质量、治疗效果及预后,而合并房颤同样

可影响COPD患者的治疗策略和预后。目前,合并COPD的房颤患者的综合管理在临床中常被忽视。本文从流行病学特点、病理生理学机制、患者管理、转归及预后等方面系统总结房颤合并COPD的相关研究进展,旨在为临床上房颤合并COPD患者的综合管理和个体化治疗提供依据。

1 流行病学特点

COPD是房颤常见并发症之一,二者有着共

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同的发病危险因素,如高龄、吸烟、男性等^[1,6,8]。Romiti等^[5]的meta分析结果显示,在46个临床研究的420万例房颤患者中,合并COPD的比例为13.0%,高于普通人群COPD的患病率。我国一项多中心前瞻性注册研究发现,有11.5%的房颤患者合并COPD^[9]。此外,COPD患者发生房颤的风险明显增加。一项前瞻性队列研究发现,COPD患者的房颤风险增加了28%^[10]。还有研究发现,房颤发生率与COPD患者气流受限的严重程度呈正相关;患者肺功能中第一秒用力呼气量每下降500ml,房颤的发生风险增加21%^[11]。COPD相关的房颤风险在CHA₂DS₂-VASc评分较低的患者中更为明显,合并COPD可使评分<2分的患者房颤发生率增高近5倍^[12]。此外,COPD急性发作会使房颤的风险进一步增加,COPD急性发作超过2次/年可使房颤的发生风险增加2倍^[10]。

2 病理生理学机制

COPD促进房颤发生的病理生理机制推测与以下因素有关:(1)COPD导致的慢性心房重构为房颤的发生和维持提供了基础;(2)COPD急性发作增加了房颤发生的风险;(3)COPD治疗用药、并发症及相关危险因素具有致心律失常的作用。

COPD患者的通气和换气功能障碍可引起低氧血症和高碳酸血症,促进肺血管收缩和肺动脉高压,进而引发心脏舒张功能障碍和心脏结构改变^[13]。慢性低氧血症还可促进低氧诱导因子的表达,引起氧化应激及全身性炎症反应,进而促进心房发生纤维化^[10,14]。COPD患者本身也普遍存在交感神经的过度激活,导致心房自律性增高,促进了房颤的发生^[15],此外,COPD导致的解剖和电重构也有利于房颤的发生和维持^[10,16]。

房颤的发作常与COPD急性加重相关。在COPD急性加重期间,过度通气和气流受限会造成胸腔内压力变化、低氧血症和酸碱平衡紊乱,这些因素共同形成了致心律失常的基础^[10]。胸腔内压力变化可导致心房跨壁压力和心肌张力改变,从而增加了心房的易损性^[10]。COPD急性发作期间出现的血氧及二氧化碳水平波动更容易导致心房肌细胞兴奋性和传导性的各向异性,影响有效不应期和动作电位时程,导致心律失常的发生风险增加^[17-18]。

治疗COPD常需使用拟交感神经药物(β_2 受体激动剂)和副交感神经阻滞药物(抗胆碱能药物),这些药物会引起自主神经系统功能失调^[15]。COPD患者常存在多种合并症,如睡眠呼吸暂停、充血性心力衰竭及高血压等,这些疾病均与心房重构过程密切相关^[9,14,19-20]。此外,COPD的常见危险因素如吸

烟、高龄等,也对房颤的发生发展有重要影响^[4]。

3 房颤患者合并COPD的管理

房颤与COPD互相影响了彼此的治疗方案和治疗效果。COPD患者合并房颤时,在治疗过程中应注意药物的致心律失常风险及对心血管病预后的影响;同样,合并COPD也使房颤患者的节律控制、室率控制和抗凝治疗更加复杂。现有的指南和共识尽管并未对此类患者的治疗策略提供详细的推荐意见^[1,8],但强调了对此类患者应重视学科交叉及两种疾病的综合管理。

3.1 呼吸道管理 良好的呼吸道症状控制是房颤合并COPD患者治疗的基础。呼吸道管理包括COPD急性加重期和稳定期的管理。COPD急性发作时的低氧和CO₂潴留会增加患者心律失常的发生风险^[17-18]。2019年更新的美国房颤管理指南推荐,当房颤患者出现COPD急性发作时,控制房颤前首先应考虑纠正低氧血症和酸中毒^[21]。在COPD稳定期的治疗药物中,茶碱类药物和 β_2 受体激动剂诱发房颤的风险较高,可能导致患者的心室率难以得到有效控制;相比之下,抗胆碱能类药物致心律失常的风险更低^[22-23]。对于伴有心血管疾病的COPD患者,吸入性的支气管舒张剂和糖皮质激素均具有良好的安全性,复合临床终点事件风险未见明显增加^[24-25]。

3.2 节律控制 合并COPD使房颤患者的节律控制面临挑战。在此类患者的节律控制方面,应注意以下几点:(1)COPD可增加房颤患者射频消融和电复律后的复发风险^[26-27];(2)对于处于COPD急性期的房颤患者,纠正呼吸失代偿之前进行药物复律治疗可能无效^[21];(3)对接受电复律治疗的房颤患者实施镇静的过程中,合并COPD者可能面临着更高的呼吸抑制和CO₂潴留风险。此外,由于胺碘酮可增加COPD患者的肺毒性和肺纤维化风险,因此,应慎用于合并COPD的房颤患者^[28]。

3.3 室率控制 房颤时心室率控制不良可能进一步加重COPD患者的呼吸困难症状^[17]。在房颤合并COPD患者的心室率控制方面,尽管此类患者普遍因为其他心血管并发症更需要接受 β 受体阻滞剂治疗,但临床上常因担心诱发支气管痉挛而减少了 β 受体阻滞剂的使用比例^[29]。但Yang等^[30]近期发表的meta分析结果显示,与安慰剂相比, β 受体阻滞剂不仅不会导致COPD患者的肺功能恶化,而且可使患者的全因死亡风险降低30%,为 β 受体阻滞剂在COPD患者中的应用提供了有力证据。COPD患者发生房颤时如需使用 β 受体阻滞剂治疗,应首选选择性 β_1 受体阻滞剂,因其不仅可降低COPD急性发

作的风险,还可消除由支气管扩张剂引起的心率加快^[31]。相比之下,洋地黄类药物对于此类患者的预后无改善作用^[31]。此外,对于重度COPD或伴有支气管痉挛的COPD患者,2020年ESC房颤管理指南推荐将非二氢吡啶类钙离子拮抗剂作为控制房颤心室率的一线药物^[1]。

3.4 抗凝治疗 预防血栓栓塞是房颤患者管理策略的重要组成部分。现有证据表明,合并COPD使房颤患者的血栓和出血风险均明显增加^[5],因此,制定更为合理的抗凝治疗方案对于合并COPD的房颤患者尤为重要。然而,当前临床指南并未推荐针对合并COPD的房颤患者的抗凝方案,因此尚需要更多的临床证据来指导其抗凝管理策略。

4 临床转归及预后

4.1 合并COPD对房颤患者预后的影响 合并COPD与房颤患者的预后不良密切相关。多个研究证实合并COPD导致房颤患者症状更重、生活质量更差,同时血栓及出血风险明显增加^[5,32]。一项多中心前瞻性真实世界研究将3119例房颤患者按照是否合并COPD进行分组分析,发现合并COPD的房颤患者存在较多的心血管病危险因素及并发症负担,如高龄、吸烟、糖尿病、冠心病、心力衰竭等,导致其生活质量评分较低^[29]。此外,合并COPD患者的CHA2DS2-VASc评分和HAS-BLED评分往往高于无COPD的患者,这意味着合并COPD者存在较高的血栓和出血风险^[32]。Romiti等^[5]的荟萃分析结果支持了上述推测,发现与无COPD的房颤患者相比,合并COPD的房颤患者发生缺血性卒中的风险增加了26%,主要出血事件风险增加了45%;进一步的亚组分析结果显示,合并COPD明显增加了年轻患者的卒中风险,可能与这些患者因较低的CHA2DS2-VASc评分而未接受抗凝治疗有关。

COPD也是导致房颤患者复发率、再入院率和死亡发生率增高的重要因素^[26-27,33]。Pisters等^[26]对712例电复律后的房颤患者进行了为期1年的随访,结果发现,合并COPD为房颤复发的独立危险因素。Arora等^[27]的研究也表明,合并COPD可增加房颤患者消融术后复发的风险。因此,COPD也被纳入为HATCH评分的一部分,用于评价房颤复发和进展的风险^[34-35]。Hirayama等^[36]对944例房颤患者进行研究发现,COPD急性发作后90 d内的房颤发生率明显升高,因房颤再住院的风险增加了近2倍。Proietti等^[29]发现,合并COPD的房颤患者全因死亡发生率(12.8% vs. 5.4%, $P<0.001$)和心血管疾病死亡发生率(6.3% vs. 2.3%, $P<0.001$)均高于无COPD者,

且在校正传统心血管病危险因素后,合并COPD仍是全因死亡风险和心血管病死亡风险增加的独立预测因子。Romiti等^[5]的研究也支持这一结论,该研究中合并COPD可使全因死亡风险增加2.2倍(95%CI 1.93~2.55),心血管病死亡风险增加1.8倍(95%CI 1.39~2.43)。

4.2 合并房颤对COPD患者预后的影响 房颤同样也可影响COPD患者的临床转归。有研究发现,房颤可导致心房收缩功能受损,肺血管阻力升高,使COPD患者心肺功能进一步恶化,是COPD患者发生心力衰竭的独立预测因子^[37-38]。此外,房颤可使COPD患者心血管病死亡风险增加9.7倍,且相比于阵发性房颤,持续性房颤对COPD患者预后的影响更为明显^[37]。

5 总结与展望

COPD是房颤患者的重要并发症,可通过多种病理生理机制促进房颤的发生和发展。房颤与COPD互相影响着彼此的预后和转归,了解房颤与COPD的相互影响对于指导临床治疗、改善患者预后具有重要意义。此外,针对房颤合并COPD患者的特点,制定出有效的多学科综合管理模式和个体化治疗方案至关重要。对于合并COPD的房颤患者,需要进行包括呼吸道管理、节律控制、室率控制和抗凝治疗在内的综合管理。但房颤患者是否需要常规筛查COPD,合并COPD时是否需要调整抗凝治疗策略,这些问题仍有待进一步研究,未来仍需通过大型前瞻性队列研究来评估这些治疗方案的临床获益情况。

【参考文献】

- [1] Hindricks G, Potpara T, Dagres N, *et al.* 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC[J]. *Eur Heart J*, 2021, 42(5): 373-498.
- [2] Zhang ZX, Ma CS. Comprehensive management of atrial fibrillation[J]. *Chin J Pract Intern Med*, 2020, 40(3): 177-181. [张筑欣, 马长生. 心房颤动的综合管理[J]. *中国实用内科杂志*, 2020, 40(3): 177-181.]
- [3] Zeng XJ, Wen HZ, Zhu HH, *et al.* Correlation between atrial arrhythmia and V1 lead P wave terminal potential and left atrial diameter in patients with obstructive sleep apnea syndrome[J]. *Med J Chin PLA*, 2020, 45(6): 627-632. [曾晓杰, 温华知, 朱红红, 等. 阻塞性睡眠呼吸暂停综合征患者房性心律失常与V₁导联P波终末电势及左心房直径的相关性[J]. *解放军医学杂志*, 2020, 45(6): 627-632.]
- [4] Labaki WW, Rosenberg SR. Chronic obstructive pulmonary

- disease[J]. *Ann Intern Med*, 2020, 173(3): ITC17-ITC32.
- [5] Romiti GF, Corica B, Pipitone E, *et al.* Prevalence, management and impact of chronic obstructive pulmonary disease in atrial fibrillation: a systematic review and meta-analysis of 4,200,000 patients[J]. *Eur Heart J*, 2021, 42(35): 3541-3554.
- [6] Ye J, Yao P, Shi X, *et al.* A systematic literature review and meta-analysis on the impact of COPD on atrial fibrillation patient outcome[J]. *Heart Lung*, 2022, 51: 67-74.
- [7] Zeng XJ, Wen HZ, Zhu HH, *et al.* Correlation between atrial arrhythmia and V1 lead P wave terminal potential and left atrial diameter in patients with obstructive sleep apnea syndrome[J]. *Med J Chin PLA*, 2020, 45(6): 627-632.[曾晓杰, 温华知, 朱红红, 等. 阻塞性睡眠呼吸暂停综合征患者房性心律失常与V1导联P波终末电势及左心房直径的相关性[J]. *解放军医学杂志*, 2020, 45(6): 627-632.]
- [8] Singh D, Agusti A, Anzueto A, *et al.* Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019[J]. *Eur Respir J*, 2019, 53(5): 1900164.
- [9] Huang B, Yang Y, Zhu J, *et al.* Clinical characteristics and prognostic significance of chronic obstructive pulmonary disease in patients with atrial fibrillation: results from a multicenter atrial fibrillation registry study[J]. *J Am Med Dir Assoc*, 2014, 15(8): 576-581.
- [10] Grymonprez M, Vakaet V, Kavousi M, *et al.* Chronic obstructive pulmonary disease and the development of atrial fibrillation[J]. *Int J Cardiol*, 2019, 276: 118-124.
- [11] Chahal H, Heckbert SR, Barr RG, *et al.* Ability of reduced lung function to predict development of atrial fibrillation in persons aged 45 to 84 years (from the multi-ethnic study of atherosclerosis-lung study)[J]. *Am J Cardiol*, 2015, 115(12): 1700-1704.
- [12] Perticone M, Sciacqua A, Tripepi G, *et al.* Competitive interaction between chronic obstructive pulmonary disease and CHA2DS2-VASc score in predicting incident atrial fibrillation[J]. *Int J Cardiol*, 2018, 255: 74-79.
- [13] Elia D, Caminati A, Zompatori M, *et al.* Pulmonary hypertension and chronic lung disease: where are we headed? [J]. *Eur Respir Rev*, 2019, 28(153): 190065.
- [14] Linz D, McEvoy RD, Cowie MR, *et al.* Associations of obstructive sleep apnea with atrial fibrillation and continuous positive airway pressure treatment: a review[J]. *JAMA Cardiol*, 2018, 3(6): 532-540.
- [15] Linz D, Ukena C, Mahfoud F, *et al.* Atrial autonomic innervation: a target for interventional antiarrhythmic therapy?[J]. *J Am Coll Cardiol*, 2014, 63(3): 215-224.
- [16] Alter P, Watz H, Kahnert K, *et al.* Airway obstruction and lung hyperinflation in COPD are linked to an impaired left ventricular diastolic filling[J]. *Respir Med*, 2018, 137: 14-22.
- [17] Terzano C, Romani S, Conti V, *et al.* Atrial fibrillation in the acute, hypercapnic exacerbations of COPD[J]. *Eur Rev Med Pharmacol Sci*, 2014, 18(19): 2908-2917.
- [18] Matarese A, Sardu C, Shu J, *et al.* Why is chronic obstructive pulmonary disease linked to atrial fibrillation? A systematic overview of the underlying mechanisms[J]. *Int J Cardiol*, 2019, 276: 149-151.
- [19] Canepa M, Franssen FME, Olschewski H, *et al.* Diagnostic and therapeutic gaps in patients with heart failure and chronic obstructive pulmonary disease[J]. *JACC Heart Fail*, 2019, 7(10): 823-833.
- [20] Baumert M, Immanuel SA, Stone KL, *et al.* Composition of nocturnal hypoxaemic burden and its prognostic value for cardiovascular mortality in older community-dwelling men[J]. *Eur Heart J*, 2020, 41(4): 533-541.
- [21] January CT, Wann LS, Calkins H, *et al.* 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration with the Society of Thoracic Surgeons[J]. *Circulation*, 2019, 140(2): e125-e151.
- [22] Shin SY, Manuel ARG, Lip GYH. Atrial fibrillation and end-stage COPD: a close association revisited[J]. *Chest*, 2019, 155(5): 888-889.
- [23] Lahousse L, Verhamme KM, Stricker BH, *et al.* Cardiac effects of current treatments of chronic obstructive pulmonary disease[J]. *Lancet Respir Med*, 2016, 4(2): 149-164.
- [24] Brook RD, Anderson JA, Calverley PM, *et al.* Cardiovascular outcomes with an inhaled beta2-agonist/corticosteroid in patients with COPD at high cardiovascular risk[J]. *Heart*, 2017, 103(19): 1536-1542.
- [25] Wise RA, Chapman KR, Scirica BM, *et al.* Effect of acclidinium bromide on major cardiovascular events and exacerbations in high-risk patients with chronic obstructive pulmonary disease: the ASCENT-COPD randomized clinical trial[J]. *JAMA*, 2019, 321(17): 1693-1701.
- [26] Pisters R, Nieuwlaat R, Prins MH, *et al.* Clinical correlates of immediate success and outcome at 1-year follow-up of real-world cardioversion of atrial fibrillation: the Euro Heart Survey[J]. *Europace*, 2012, 14(5): 666-674.
- [27] Arora S, Lahewala S, Tripathi B, *et al.* Causes and predictors of readmission in patients with atrial fibrillation undergoing catheter ablation: a national population-based cohort study[J]. *J Am Heart Assoc*, 2018, 7(12): e009294.
- [28] Colunga Biancatelli RM, Congedo V, Calvosa L, *et al.* Adverse reactions of amiodarone[J]. *J Geriatr Cardiol*, 2019, 16(7): 552-566.
- [29] Proietti M, Laroche C, Drozd M, *et al.* Impact of chronic obstructive pulmonary disease on prognosis in atrial fibrillation: a report from the EUR Observational Research Programme Pilot Survey on Atrial Fibrillation (EORP-AF) General Registry[J]. *Am Heart J*, 2016, 181: 83-91.
- [30] Yang YL, Xiang ZJ, Yang JH, *et al.* Association of β -blocker use with survival and pulmonary function in patients with chronic obstructive pulmonary and cardiovascular disease: a systematic review and meta-analysis[J]. *Eur Heart J*, 2020, 41(46): 4415-4422.
- [31] Rodríguez-Mañero M, López-Pardo E, Cordero A, *et al.* A prospective study of the clinical outcomes and prognosis associated with comorbid COPD in the atrial fibrillation population[J]. *Int J Chron Obstruct Pulmon Dis*, 2019, 14: 371-380.
- [32] Durheim MT, Holmes DN, Blanco RG, *et al.* Characteristics and outcomes of adults with chronic obstructive pulmonary disease and atrial fibrillation[J]. *Heart*, 2018, 104(22): 1850-1858.
- [33] Desai R, Patel U, Singh S, *et al.* The burden and impact of

- arrhythmia in chronic obstructive pulmonary disease: insights from the National Inpatient Sample[J]. *Int J Cardiol*, 2019, 281: 49-55.
- [34] Malavasi VL, Fantecchi E, Tordoni V, *et al.* Atrial fibrillation pattern and factors affecting the progression to permanent atrial fibrillation[J]. *Intern Emerg Med*, 2021, 16(5): 1131-1140.
- [35] Emren SV, Kocabaş U, Duygu H, *et al.* The role of HATCH score in predicting the success rate of sinus rhythm following electrical cardioversion of atrial fibrillation[J]. *Kardiol Pol*, 2016, 74(9): 978-984.
- [36] Hirayama A, Goto T, Shimada YJ, *et al.* Acute exacerbation of chronic obstructive pulmonary disease and subsequent risk of emergency department visits and hospitalizations for atrial fibrillation[J]. *Circ Arrhythm Electrophysiol*, 2018, 11(9): e006322.
- [37] Tomioka T, Fukui K, Tanaka S, *et al.* Influence of atrial fibrillation on cardiac prognosis in chronic obstructive pulmonary disease[J]. *Indian Heart J*, 2019, 71(1): 7-11.
- [38] Huang Q, Xiong H, Shuai T, *et al.* Risk factors for new-onset atrial fibrillation in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis[J]. *PeerJ*, 2020, 8: e10376.

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