The Delphian lymph node in thyroid cancer[J]. Ann Surg,2008,247:477－482.
[16] THALER E R,MONTONE K, TUCKER J, et al. Delphian lymph node in laryngeal carcinoma: a whole organ study[J]. Laryngoscope,1997,107:332－334.
[17] ISAACS J D, MCMULLEN T P, SIDHU S B,et al. Predictive value of the Delphian and level VI nodes in papillary thyroid cancer[J]. ANZ J Surg,2010,80:834－838.
[18] IYER N G, KUMAR A, NIXON I, et al. Incidence and significance of Delphian node metastasis in papillary thyroid cancer[J]. Ann Surg,2011, 253:988－991.
[19] LEE Y C, SHIN S Y, KWON K H,et al. Incidence and clinical characteristics of prelaryngeal lymph node metastasis in papillary thyroid cancer[J]. Eur Arch Otorhinolaryngol,2013,270:2547－2550.
[20] KIM W W, YANG S I, KIM J H, et al. Experience and analysis of Delphian lymph node metastasis in patients with papillary thyroidcarcinoma[J]. World J Surg Oncol, 2012,10:226－232.
[21] BAEK S K,JUNG K Y,KANG S M,et al. Clinical risk factors associ-ated with cervical lymph node recurrence in papillary thyroid carcinoma[J]. Thyroid, 2010,20:147－152.
[22] LEE Y C, SHIN S Y, KWON K H, et al. Incidence and clinical characteristics of prelaryngeal lymph node metastasis in papillary thyroid cancer[J]. Eur Arch Otorhinolaryngol,2013, 270:2547－2550.
[23] 刘永锋.加强分化型甲状腺癌的规范化治疗[J]. 中国普外基础与临床杂志,2009,16(5):341－343.

(收稿日期:2014-07-18)

阻塞性睡眠呼吸暂停低通气综合征与支气管哮喘关系的研究进展

王金凤[1] 谢宇平[1] 马薇[1] 侯一平[2] 惠培林[1] 赵丽君[1] 魏晓泉[1]

[关键词] 睡眠呼吸暂停低通气综合征,阻塞性;哮喘;持续气道正压通气
doi:10.13201/j.issn.1001-1781.2015.04.027
[中图分类号] R563.8 [文献标志码] A

The research progress of relationship between the obstructive sleep apnea hypopnea syndrome and asthma

Summary Obstructive sleep apnea hypopnea syndrome (OSAHS) is characterized by repeated episodes of upper airway obstruction that results in brief periods of breathing cessation (apnea) or a marked reduction in airflow (hypopnea) during sleep. Asthma is a chronic inflammatory disease of the airways characterized by revesible airflow obstruction and bronchial hyperresponsiveness. This article reviewed related reseaches progress of relationship between the obstructive sleep apnea hypopnea syndrom and asthma in the vascular endothelial growth factor, systemic inflammation, leptin, obesity, gastroesophageal reflux disease and upper airway diseases, excessive daytime sleepiness and asthma control.

Key words sleep apnea hypopnea syndrome, obstructive; asthma; continuous positive airway pressure

阻塞性睡眠呼吸暂停低通气综合征(OSAHS)是睡眠期反复出现间断性的上气道阻塞引起以打鼾、呼吸暂停、呼吸浅慢、睡眠中断、低氧血症,以及日间嗜睡等为特征的临床综合征。支气管哮喘是由多种细胞和细胞组分参与的气道慢性炎症性疾病,这种慢性炎症导致气道反应性增加并出现广泛多变的可逆性气流受限,并引起反复发作性的喘息、气急、胸闷或咳嗽等症状,常在夜间和(或)清晨发作、加剧。OSAHS 与支气管哮喘是目前严重威胁人类健康的两种疾病,越来越多的研究显示两种疾病之间存在密切的联系。研究显示 OSAHS 伴哮喘者达到 52%,其中重度哮喘达到 33.6%[1],哮喘患者经多导睡眠呼吸监测提示 AHI>5 次/h 达到 66%,AHI>15/h 达到 43%[2]。本文将 OSAHS 与支气管哮喘相同的病理生理状态、病因、临床症状及相互影响等方面在国内外最新研究现状进行综述。

1 OSAHS、支气管哮喘与血管内皮生长因子

OSAHS 与支气管哮喘患者微血管出现内皮细胞增殖、血管增生、通透性增加等病理性改变,均与机体组织内血管内皮生长因子(vascular

[1]甘肃省人民医院睡眠医学中心(兰州,730000)
[2]兰州大学基础医学院
通信作者:谢宇平,E-mail:xyp5894@163.com

endothelial growth factor，VEGF）的表达增加相关。

OSAHS 与支气管哮喘均会造成机体组织严重的缺氧，而缺氧是调控 VEGF 在体内的合成及活性的重要因子，可通过改变细胞的氧化还原状态，导致体内缺氧诱导因子-1α 积聚，从而诱导 VEGF 的表达[3]。目前国内外的研究均显示，OSAHS 患者血浆 VEGF 浓度明显高于正常对照组，且与 AHI、夜间缺氧时间呈正相关，经有效持续气道正压通气（continuous positive airway pressure，CPAP）治疗后者 VEGF 水平明显下降[4-5]。同时研究发现轻、中、重度哮喘患者的气道黏膜下层和（或）黏膜固有层均有血管密度（单位面积内的血管数）和血管面积（单位面积内血管所占面积）的增加，且上述改变的程度与哮喘的严重程度相平行，同时发现用力呼气容积（forced expiratory volume，FEV）与中气道血管数目呈负相关[6-7]。

2 OSAHS、支气管哮喘与系统性炎症

OSAHS 患者由于夜间低氧血症、高碳酸血症及睡眠片段化，从而增加机体交感神经的兴奋性及氧化应激反应，从而使机体处于前炎症状态[8]。Kheirandish-Gozal 等[9]通过研究发现，OSAHS 患儿在腺样体及扁桃体切除后，体内甘油三酯及 C 反应蛋白水平明显下降，提示 OSAHS 能够降低脂质代谢，加重系统性炎症反应。

TNF-α 是一种重要的前炎症因子，它可以影响气道平滑肌的收缩性，在哮喘的发病机制中发挥重要作用[10]。同时 TNF-α 也是睡眠呼吸紊乱的一个重要标志物，OSAHS 成年患者经 CPAP 治疗后 TNF-α 水平也明显下降[8]。TNF-α 抑制物可以减轻 OSAHS 的严重性[11]。中、重度 OSAHS 患儿行腺样体及扁桃体切除术后，TNF-α 水平明显下降[12]。

3 OSAHS、支气管哮喘与瘦素

研究证实，体内瘦素在 OSAHS 发病机制中发挥重要的作用，同时越来越多的研究显示支气管哮喘与瘦素亦密切相关。OSAHS 经 CPAP 治疗后 AHI 指数从 29 次/h 降到 1.6 次/h，瘦素水平从 8.5 ng/min 降到 7.4 ng/min[13]。Chen 等[14]研究显示，哮喘患儿体内瘦素水平是非哮喘患儿的 2 倍。Guler 等[15]经逐步 Logistic 回归分析发现瘦素水平是哮喘的危险预测因子。

4 OSAHS、支气管哮喘与肥胖

研究证实，肥胖是患 OSAHS 的高危因素，与 AHI 呈正相关。而同时 OSAHS 也可以干扰脂质稳态，导致肥胖[16]。目前许多研究发现，肥胖也与哮喘密切相关。Cottrell 等[17]在研究中发现，17 994例 OSAHS 患儿中 14％患有哮喘，且患病率与体质指数呈正相关。

进一步的研究发现，OSAHS 由于刺激体重增加，可以加重哮喘的症状，在哮喘的严重性中发挥重要的作用，哮喘患者呼出一氧化氮的降低与体质指数、瘦素、脂肪链接蛋白的水平相关[18]。

5 OSAHS、支气管哮喘与胃食管反流病

胸腔负压的增加会导致胃内容的反流，不仅与 OSAHS 密切相关，而且在哮喘发病中发挥重要的作用[19]。

OSAHS 患者在睡眠中发生呼吸事件时，呼吸努力的增加导致胸腔负压的增加，从而导致胃食管反流。研究显示，71.6％的 OSAHS 患者同时患有胃食管反流病（监测是采用食管 PH 测试），且其中 10.4％的患者无相关症状[20]。Guda 等[21]进一步研究证明，患胃食管反流病患者较无胃食管反流病患者 OSAHS 的症状更重。

胃食管反流可以导致气道的高反应性，增加哮喘的控制难度，在临床中却常被忽略。哮喘患者胃食管反流病的患病率达 84％[22]。通过外科手术方法积极治疗胃食管反流病可显著控制哮喘。Sontag 等[23]研究了 62 例哮喘伴胃食管反流病的患者，发现经外科手术治疗后患者夜间喘息、咳嗽及低氧血症的发生率立即下降，且经两年随访发现，外科手术组哮喘症状的缓解率达到 74.5％，而抑酸治疗组只达到 9.1％。

6 OSAHS、支气管哮喘与上气道疾病

鼻咽部属于上气道一部分，鼻咽部多种疾病不仅参与 OSAHS 发病，且与哮喘密切相关。

儿童 OSAHS 最常见的原因是腺样体肥大，慢性扁桃体炎，慢性鼻炎，鼻中隔偏曲[24]。Donnelly 等[25]应用核磁共振成像显示，81％的 OSAHS 患儿在睡眠过程中发生咽部塌陷。中度 OSAHS 患儿经氟莫特罗治疗 6 周后，睡眠呼吸指数明显改善，其中 54.1％的患儿 AHI 恢复正常[26]。

变应性鼻炎是哮喘的独立危险因素，哮喘患者患变应性鼻炎的概率达到 100％[27]。Lavigne 等[28]研究显示，哮喘患儿经氟替卡松治疗 4 周后，AHI 较对照组明显下降。

7 OSAHS、支气管哮喘与白天过度嗜睡

OSAHS 和哮喘都会导致睡眠的片段化及白天过度嗜睡，白天过度嗜睡症与 OSAHS 及哮喘密切相关。Calhoun 等[29]研究 700 例儿童发现，13.3％具有白天过度嗜睡症状的患儿同时患有支气管哮喘。研究显示，导致白天嗜睡症的危险因子是腰围（$OR=1.4$）和哮喘病史（$OR=2.9$）。

OSAHS 患者夜间频繁的觉醒与夜间气流受限和低氧血症导致的呼吸相关努力增加相关[30]。哮喘患者睡眠的片段化、早醒、睡眠维持障碍及白天过度嗜睡与夜间气道口径减小、频繁咳嗽及呼吸困难相关[31]。进一步研究发现，哮喘患者茶碱的应用

与入睡困难、睡眠效率下降相关，FEV1 与白天乏力呈负相关，呼气峰值流速（peak expiratory flow）与失眠持续时间及睡眠效率呈正相关[32]。

8 OSAHS 和哮喘的控制

OSAHS 与支气管哮喘可相互增加疾病的严重性及控制难度。OSAHS 患者患难治性哮喘的概率比正常人增加 3.6 倍[33]，这可能与 OSAHS 患者在睡眠过程中发生呼吸紊乱时胸腔负压增加，导致胃食管反流，从而导致气道高反应性及支气管炎症有关[34]。同时研究显示约 63%的重度哮喘患儿患有 OSAHS[35]。进一步研究发现哮喘程度越重 AHI 越高（重度、中度、轻度哮喘患者的 AHI 分别为 23.6、19.5 和 9.9，$P<0.01$），且 OSAHS 伴重度哮喘患者夜间平均血氧饱和度较单纯 OSAHS 者更低，尤其在快速眼动期[36-37]。

OSAHS 伴支气管哮喘患者，经 CPAP 治疗后夜间哮喘症状明显缓解[38-39]。支气管哮喘需要长期吸入激素治疗，但目前有研究显示常规吸入低剂量、中等剂量、高剂量的糖皮质激素患者，较未吸入激素治疗的哮喘患者发展为 OSAHS 的概率分别是 2.29 倍，3.67 倍和 5.43 倍，且 FEV1 与 OSAHS 严重性呈负相关，可能与吸入糖皮质激素造成上气道结构的增生有关[40]。

9 展望

OSAHS 与哮喘同为呼吸道的疾病，具有高 VEGF、炎症因子、瘦素等相似的病理生理状态，肥胖、胃食管反流病及上气道疾病等相同的病因，白天过度嗜睡共同的临床症状。同时两种疾病之间可相互影响，OSAHS 伴哮喘时应用 CPAP 治疗可降低气道及系统性炎症反应，减低气道高反应性，抑制瘦素的产生，改善睡眠结构，降低体重，提高心功能及减少胃管反流，降低急性发作的次数和难治性哮喘的比率[41]。目前研究显示 OSAHS 与哮喘两种疾病之间存在密切的关系，但具体病理机制尚不清楚。对两种疾病共同的病理机制的探讨，将增进对两种疾病的认识，从而有可能为两种疾病的治疗提供新的方法。

参考文献

[1] GUVEN S F, DURSUN A B, CIFTCI B, et al. The prevalence of obstructive sleep apnea in patients with difficult-to-treat asthma[J]. Asian Pac J Allergy Immunol, 2014, 32:153－159.

[2] BYUN M K, PARK S C, CHANG Y S, et al. Associations of moderate to severe asthma with obstructive sleep apnea[J]. Yonsei Med J, 2013, 54: 942－948.

[3] LI J, LI C, CHAI L, et al. Relationship between plasma vascular endothelial growth factor and tumor necrosis factor-alpha and obstructive sleep apnea hypopnea syndrome in children[J]. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi, 2014, 49:44－48.

[4] CIFTCI T U, KOKTURK O, DEMIRTAS S, et al. Consequences of hypoxia-reoxygenation phenomena in patients with obstructive sleep apnea syndrome[J]. Ann Saudi Med, 2011, 31: 14－18.

[5] LAVIE L, KRAICZI H, HEFETZ A, et al. Plasma vascular endothelial growth factor in sleep apnea syndrome: effects of nasal continuous positive air pressure treatment[J]. Am J Respir Crit Care Med, 2002, 165: 1624－1628.

[6] HARKNESS L M, KANABAR V, SHARMA H S, et al. Pulmonary vascular changes in asthma and COPD[J]. Pulm Pharmacol Ther, 2014, 29: 144－155.

[7] HOSHINO M, TANAKA H, ABE S. Quantitative analysis of bronchial wall vascularity in the medium and small airways of patients with asthma and COPD[J]. Chest, 2005, 127: 965－972.

[8] SOOSE R J. Role of allergy in sleep-disordered breathing[J]. Otolaryngol Clin North Am, 2011, 44: 625－635.

[9] KHEIRANDISH-GOZAL L, PERIS E, WANG Y, et al. Lipopolysaccharide-binding protein plasma levels in children: effects of obstructive sleep apnea and obesity[J]. J Clin Endocrinol Metab, 2014, 99: 656－663.

[10] BAESSLER A, NADEEM R, HARVEY M, et al. Treatment for sleep apnea by continuous positive airway pressure improves levels of inflammatory markers-a meta-analysis[J]. J Inflamm (Lond), 2013, 10: 13－13.

[11] VGONTZAS A N, ZOUMAKIS E, BIXLER E O, et al. Selective effects of CPAP on sleep apnoea-associated manifestations[J]. Eur J Clin Invest, 2008, 38: 585－595.

[12] GOZAL D, SERPERO L D, KHEIRANDISH-GOZAL L, et al. Sleep measures and morning plasma TNF-alpha levels in children with sleep-disordered breathing[J]. Sleep, 2010, 33: 319－325.

[13] SÁNCHEZ-DE-LA-TORRE M, MEDIANO O, et al. The influence of obesity and obstructive sleep apnea on metabolic hormones[J]. Sleep Breath, 2012, 16: 649－656.

[14] CHEN Y C, DONG G H, LIN K C, et al. Gender difference of childhood overweight and obesity in predicting the risk of incident asthma: a systematic review and meta-analysis[J]. Obes Rev, 2013, 14: 222－231.

[15] GULER N, KIRERLERI E, ONES U, et al. Leptin: does it have any role in childhood asthma[J]? J Allergy Clin Immunol, 2004, 114: 254－259.

[16] ALKHALIL M, SCHULMAN E, GETSY J. Obstructive sleep apnea syndrome and asthma: what are the links[J]? J Clin Sleep Med, 2009, 5:71－78.

[17] COTTRELL L, NEAL W A, ICE C, et al. Piedimonte G. Metabolic abnormalities in children with

asthma[J]. Am J Respir Crit Care Med, 2011, 183: 441－448.

[18] HOLGUIN F, ROJAS M, BROWN L A, et al. Airway and plasma leptin and adiponectin in lean and obese asthmatics and controls[J]. J Asthma, 2011, 48: 217－223.

[19] ALKHALIL M, SCHULMAN E, GETSY J. Obstructive sleep apnea syndrome and asthma: what are the links[J]? J Clin Sleep Med, 2009,5:71－78.

[20] SAMELSON C F. Gastroesophageal reflux and obstructive sleep apnea[J]. Sleep, 1989,12:475－476.

[21] GUDA N, PARTINGTON S, VAKIL N. Symptomatic gastro-oesophageal reflux, arousals and sleep quality in patients undergoing polysomnography for possible obstructive sleep apnoea[J]. Aliment Pharmacol Ther, 2004, 20: 1153－1159.

[22] ISHIZUKA T, HISADA T, KAMIDE Y, et al. The effects of concomitant GERD, dyspepsia, and rhinosinusitis on asthma symptoms and FeNO in asthmatic patients taking controller medications[J]. J Asthma Allergy, 2014, 5: 131－139.

[23] SONTAG S J, O'CONNELL S, KHANDELWAL S, et al. Asthmatics with gastroesophageal reflux: long term results of a randomized trial of medical and surgical antireflux therapies[J]. Am J Gastroenterol, 2003, 98: 987－999.

[24] COUSSENS S, BAUMERT M, KOHLER M, et al. Movement distribution: a new measure of sleep fragmentation in children with upper airway obstruction [J]. Sleep,2014,37:2025－2034.

[25] DONNELLY L F, CASPER K A, CHEN B. Correlation on cine MR imaging of size of adenoid and palatine tonsils with degree of upper airway motion in asymptomatic sedated children[J]. AJR Am J Roentgenol, 2002,179: 503－508.

[26] KHEIRANDISH-GOZAL L, GOZAL D. Intranasal budesonide treatment for children with mild obstructive sleep apnea syndrome[J]. Pediatrics, 2008, 122: e149－155.

[27] CRUZ A A. The 'united airways' require an holistic approach to management[J]. Allergy, 2005, 60: 871－874.

[28] LAVIGNE F, PETROF B J, JOHNSON J R,et al. Effect of topical corticosteroids on allergic airway inflammation and disease severity in obstructive sleep apnoea[J]. Clin Exp Allergy, 2013, 43: 1124－1133.

[29] CALHOUN S L, VGONTZAS A N, FERNANDEZ-MENDOZA J, et al. Prevalence and risk factors of excessive daytime sleepiness in a community sample of young children: the role of obesity, asthma, anxiety/depression, and sleep[J]. Sleep, 2011, 34 :503－507.

[30] EKICI A, EKICI M, KURTIPEK E, et al. Association of asthma-related symptoms with snoring and apnea and effect on health-related quality of life[J]. Chest, 2005, 128: 3358－3363.

[31] CHUGH I M, KHANNA P, SHAH A. Nocturnal symptoms and sleep disturbances in clinically stable asthmatic children[J]. Asian Pac J Allergy Immunol, 2006,24:135－142.

[32] KOINIS-MITCHELL D, CRAIG T, ESTEBAN C A,et al. Sleep and allergic disease: a summary of the literature and future directions for research[J]. J Allergy Clin Immunol,2012,130:1275－1281.

[33] TEODORESCU M, POLOMIS D A, HALL S V, et al. Association of obstructive sleep apnea risk with asthma control in adults[J]. Chest, 2010, 138: 543－550.

[34] BULCUN E, EKICI M, EKICI A, et al. Bronchial hyperresponsiveness in patients with obstructive sleep apnea syndrome[J]. Tuberk Toraks, 2013, 61: 221－226.

[35] KHEIRANDISH-GOZAL L, DAYYAT E A, EID N S, et al. Obstructive sleep apnea in poorly controlled asthmatic children: effect of adenotonsillectomy[J]. Pediatr Pulmonol, 2011, 46: 913－918.

[36] GUTIERREZ M J, ZHU J, RODRIGUEZ-MARTINEZ C E, et al. Nocturnal phenotypical features of obstructive sleep apnea (OSA) in asthmatic children[J]. Pediatr Pulmonol, 2013, 48: 592－600.

[37] JULIEN J Y, MARTIN J G, ERNST P, et al. Prevalence of obstructive sleep apnea-hypopnea in severe versus moderate asthma[J]. J Allergy Clin Immunol, 2009,124: 371－376.

[38] PRASAD B, NYENHUIS S M, WEAVER T E. Obstructive sleep apnea and asthma: associations and treatment implications. Sleep[J]. Med Rev, 2014, 18: 165－171.

[39] SUNDAR K M, DALY S E, WILLIS A M. A longitudinal study of CPAP therapy for patients with chronic cough and obstructive sleep apnoea[J]. Cough, 2013,9:19－19.

[40] TEODORESCU M, CONSENS F B, BRIA W F, et al. Predictors of habitual snoring and obstructive sleep apnea risk in patients with asthma[J]. Chest, 2009, 135:1125－1132.

[41] GUVEN S F, DURSUN A B, CIFTCI B, et al. The prevalence of obstructive sleep apnea in patients with difficult-to-treat asthma[J]. Asian Pac J Allergy Immunol,2014, 32: 153－159.

(收稿日期:2014-09-28)