· 论著 ·

睡眠重叠综合征与糖尿病发病率的横断面调查研究

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[摘 要] **目的**:阻塞性睡眠呼吸暂停(obstructive sleep apnea, OSA)与慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)均增加冠状动脉粥样硬化性心脏病(简称冠心病)和代谢性疾病的风险,但鲜有研究关注二者合并的睡眠重叠综合征是否比单一疾病更为增加临床患病概率,本研究目的是调查睡眠重叠综合征与糖尿病发病率的相关性。**方法**:回顾2011年1月至2014年12月在北京安贞医院睡眠医学中心接受便携式睡眠监测的1 939名患者。COPD的诊断基于临床表现和肺功能,OSA的诊断需要呼吸暂停低通气指数 ≥15 次/h。研究对象被分为对照组(n=1 093)、单纯COPD组(n=62)、单纯OSA组(n=735)、重叠综合征组(n=49),使用Logistic回归模型分析糖尿病发病的相关因素。**结果**:重叠综合征患者患2型糖尿病的概率均高于对照组和单纯OSA患者(OR=5.82, 95% CI:3.23~10.48, P<0.001 和 OR=4.35, 95% CI:2.41~7.88, P<0.001)。矫正年龄、性别、体重指数等因素后差异仍有统计学意义(OR=2.69, 95% CI:1.13~6.52, P=0.026 和 OR=3.64, 95% CI:1.53~8.83, P=0.004)。年龄<58岁的患者和女性患者中,重叠综合征与2型糖尿病的发生存在独立相关性(OR=8.45, 95% CI:1.46~65.90, P=0.018 与 OR=4.39, 95% CI:1.04~22.50, P=0.044);年龄≥58岁的患者和男性患者中,重叠综合征与糖尿病发病无显著相关性。**结论**:睡眠重叠综合征与2型糖尿病的发病存在相关性,需要进一步研究证实治疗重叠综合征是否能降低代谢异常的风险,甚至减少未来并发症的概率。

[关键词] 睡眠重叠综合征;2型糖尿病;慢性阻塞性肺疾病;阻塞性睡眠呼吸暂停
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Association of sleep overlap syndrome with type 2 diabetes in a cross-sectional study

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ABSTRACT **Objective**: Growing evidence indicates that both chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) may be related to increased risk of developing metabolic disorder and cardiovascular diseases. However, the association of sleep overlap syndrome (combination of COPD and OSA) with type 2 diabetes is unclear. The aim of this study was to investigate the association between overlap syndrome and prevalence of type 2 diabetes. **Methods**: In this study, 1 939 patients who completed home sleep test from January 2011 to December 2014 in sleep center of Beijing Anzhen Hospital were retrospectively studied. Sleep events were scored by experienced sleep technicians. COPD were diagnosed according to clinical manifestation and spirometry, while OSA was defined by apnea-hypopnea index ≥15 event/h. All subjects were divided retrospectively into overlap syndrome group (n=1 093), isolated COPD group (n=62), isolated OSA group (n=735), and control group (n=49). The independent association of overlap syndrome with type 2 diabetes prevalence was estimated by using Logistic regression models. **Results**: Compared with control group and the patients with isolated OSA, the patients with overlap syndrome had significantly higher odds of type 2 diabetes (OR=5.82, 95% CI: 3.23-10.48, P<0.001 and OR=4.35, 95% CI: 2.41-7.88, P<0.001), with significance persisting after adjusting for age, sex, and body mass index as confounding factors (OR=2.69, 95% CI: 1.13-6.52, P=0.026 and OR=3.64, 95% CI: 1.53-8.83, P=0.004). Among those younger than 58 years or female subjects, overlap syndrome had independent association with type 2 diabetes (OR=8.45, 95% CI: 1.46-65.90, P=0.018 and OR=4.39, 95% CI: 1.04-22.50, P=0.044). No significant association was found in the patients ≥58 and male subjects. **Conclusion**: Sleep overlap syndrome is associated with high prevalence of type 2 diabetes. Further study is needed to verify whether treatment toward overlap syndrome may reduce risk of metabolic disorder, and even decrease long-term risk of complications of diabetes.

KEY WORDS Sleep overlap syndrome; Type 2 diabetes mellitus; Chronic obstructive pulmonary disease; Obstructive sleep apnea

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阻塞性睡眠呼吸暂停(obstructive sleep apnea, OSA)表现为夜间反复出现的呼吸暂停,伴低氧血症,白天嗜睡,未来心血管事件风险增加[1]。慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)为不可逆的通气功能障碍,严重者出现缺氧和二氧化碳潴留。目前有研究证实,OSA与COPD均增加冠状动脉粥样硬化性心脏病(简称冠心病)和代谢性疾病的风险[1-3],但目前鲜有研究关注二者合并的睡眠重叠综合征是否较单一疾病更加增加临床患病概率。本研究目的是调查睡眠重叠综合征与2型糖尿病的相关性。

1　资料与方法

1.1　临床资料

纳入标准:回顾性分析于2011年1月至2014年12月在北京安贞医院睡眠医学中心接受睡眠监测的所有患者(≥18岁)。排除标准:既往诊断为OSA并接受气道正压、手术、口腔矫治器等治疗的患者。COPD和2型糖尿病的诊断由医生根据临床表现、体征、肺功能、化验检查等确定,需符合慢性阻塞性肺疾病全球倡议(Global Initiative for Chronic Obstructive Lung Disease, GOLD)正式颁布的《慢性阻塞性肺疾病诊断、处理和预防全球策略》[4]和《中国2型糖尿病防治指南(2010年版)》[5],同时罹患OSA与COPD者诊断为睡眠重叠综合征。

1.2　睡眠监测

采用Embletter便携式睡眠呼吸监测设备(美国邦德公司)记录夜间22点至清晨6点的睡眠呼吸事件。安装导联包括:口鼻气流、呼吸热敏、经皮指端氧饱和度、呼吸感应式胸腹运动体积描记、体位、心电图监测等。采用美国睡眠医学会的标准判读呼吸事件[6],计算呼吸暂停低通气指数(apnea-hypopnea index, AHI),即平均每小时睡眠中呼吸暂停和低通气的次数,并以AHI≥15次/h作为诊断OSA的标准。所有患者被分为4组:对照组(n=1 093)、单纯COPD组(n=62)、单纯OSA组(n=735)、重叠综合征组(n=49)。

1.3　统计学分析

采用SPSS 17.0统计软件包进行统计学分析。连续变量以中位数(四分位间距)表示,分类变量以例数(百分比)表示。连续变量比较采用Kruskal-Wallis秩和检验,分类变量比较采用卡方检验。以多因素Logistic模型分析2型糖尿病的独立相关因素,年龄、性别、体重指数(body mass index,BMI)为矫正的混杂因素,P<0.05为差异有统计学意义。

2　结果

重叠综合征组的患者年龄最大,AHI最高,夜间最低血氧饱和度最低(表1),另外,重叠综合征患者的高血压(71.4%)和冠心病(44.9%)诊断率也较高。

表1　1 939例研究对象的临床特征

Table 1　Clinical characteristics of 1 939 study subjects

Items	Control (n=1 093)	Isolate COPD (n=62)	Isolate OSA (n=735)	Overlap syndrome (n=49)	P value
Age/years	56 (45, 66)	69 (59, 77)	64 (54, 73)	69 (63, 76)	<0.001
Male	531 (48.6)	38 (61.3)	507 (69.0)	31 (63.3)	<0.001
Lowest saturation/%	87 (83, 89)	84 (81, 86)	81 (76, 85)	78 (71, 84)	<0.001
AHI/(event/h)	5 (2, 8)	6 (2, 9)	32 (21, 53)	52 (25, 85)	<0.001
Body mass index/(kg/m^2)	25.9 (22.3, 30.6)	28.0 (23.5, 33.2)	28.2 (24.4, 32.3)	29.0 (26.2, 34.6)	<0.001
Diabetes	166 (15.2)	22 (35.5)	142 (19.3)	25 (51.0)	<0.001
Hypertension	394 (36.1)	37 (59.7)	377 (51.3)	35 (71.4)	<0.001
Coronary artery disease	176 (16.1)	32 (51.6)	174 (23.7)	22 (44.9)	<0.001
History of smoking	711 (65.1)	51 (82.3)	462 (62.9)	36 (73.5)	0.011
Cerebrovascular disease	26 (2.4)	1 (1.6)	40 (5.4)	2 (4.1)	0.005
Renal disease	23 (2.1)	2 (3.2)	19 (2.6)	0	0.602
Heart failure	46 (4.2)	8 (12.9)	62 (8.4)	13 (26.5)	<0.001

Data is represented by median (interquartile range) or n (%). AHI, apnea-hypopnea index; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea.

如表2所示,重叠综合征组患2型糖尿病的概率均明显高于对照组和单纯OSA患者(OR=5.82,

95% *CI*:3.23 ~ 10.48, *P* < 0.001 或 *OR* = 4.35, 95% *CI*:2.41 ~ 7.88, *P* < 0.001)。校正年龄、性别、BMI 后,重叠综合征组患 2 型糖尿病的概率仍高于对照组和单纯 OSA 患者(*OR* = 2.69, 95% *CI*:1.13 ~ 6.52, *P* = 0.026 和 *OR* = 3.64, 95% *CI*:1.53 ~ 8.83, *P* = 0.004)。

表 2 睡眠重叠综合征与 2 型糖尿病发生概率的相关性分析 (*n* = 1 939)

Table 2 Association of sleep overlap syndrome with type 2 diabetes (*n* = 1 939)

Comparison between groups	Unadjusted			Adjusted *		
	OR	95% *CI*	*P* value	*OR*	95% *CI*	*P* value
Isolate OSA *vs.* Control	1.34	1.04 – 1.71	0.023	0.74	0.52 – 1.05	0.093
Isolate COPD *vs.* Control	3.07	1.75 – 5.25	<0.001	1.65	0.81 – 3.27	0.165
Sleep overlap syndrome *vs.* Control	5.82	3.23 – 10.48	<0.001	2.69	1.13 – 6.52	0.026
Sleep overlap syndrome *vs.* Isolate OSA	4.35	2.41 – 7.88	<0.001	3.64	1.53 – 8.83	0.004
Sleep overlap syndrome *vs.* Isolate COPD	1.89	0.89 – 4.11	0.100	1.63	0.57 – 4.75	0.360

* adjusted for age, sex, body mass index. COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea.

如表 3 所示,年龄 <58 岁的患者中,校正年龄、性别和 BMI 后,重叠综合征患者 2 型糖尿病的发生概率显著高于非重叠综合征患者(*OR* = 8.45, 95% *CI*:1.46 ~ 65.90, *P* = 0.018)。女性患者中,重叠综合征患者 2 型糖尿病的发生概率亦显著高于非重叠综合征患者(*OR* = 4.39, 95% *CI*:1.04 ~ 22.50, *P* = 0.044)。年龄≥58 岁的患者和男性患者中,重叠综合征与 2 型糖尿病的患病风险增高无显著相关性。

表 3 重叠综合征与非重叠综合征患者 2 型糖尿病患病概率的比较(*n* = 1 939)

Table 3 Comparison of type 2 diabetes odds in patients with and without sleep overlap syndrome (*n* = 1 939)

Items	Unadjusted			Adjusted *		
	OR	95% *CI*	*P* value	*OR*	95% *CI*	*P* value
Age < 58 years old (*n* = 893) *	6.34	1.55 – 24.40	0.013	8.45	1.46 – 65.90	0.018
Age ≥ 58 years old (*n* = 1 046) *	3.71	1.96 – 7.07	<0.001	2.24	0.86 – 5.94	0.099
Male (*n* = 1 107) #	5.70	2.76 – 11.94	<0.001	2.46	0.85 – 7.12	0.096
Female (*n* = 832) #	3.82	1.43 – 9.85	0.009	4.39	1.04 – 22.50	0.044

* adjusted for age, sex, and body mass index; # adjusted for age and body mass index.

3 讨论

本研究的主要发现是同时诊断 COPD 与 OSA 的睡眠重叠综合征患者罹患 2 型糖尿病的概率显著升高,尤其是女性和相对年轻的患者。与单纯的 OSA 相比,睡眠重叠综合征进一步增加患 2 型糖尿病的概率。本研究提示,重叠综合征应该被纳入代谢性疾病的重要危险相关因素,接受积极干预。

OSA 作为心血管疾病和代谢性疾病的重要危险因素已被公认[1-2]。近年来,COPD 逐渐被发现与糖尿病发病有明显相关性[7-8]。COPD 患者中糖尿病的检出率为 25%[7],中国人群糖尿病的发病率为 10%[9]。COPD 相关的代谢紊乱其可能的病理生理学机制包括:缺氧、炎症、氧化应激、胰岛素抵抗、体重增加、脂肪细胞因子代谢增强等[10]。COPD 治疗过程中,激素等药物的使用也对糖代谢造成一定的影响。可以看到,OSA 与 COPD 的致病基础存在相似性,但也有不同,例如,同样是缺氧,OSA 导致间歇性夜间低氧血症,而 COPD 导致持续低氧伴二氧化碳潴留,因此,COPD 与 OSA 具有协同的致病效应,即可解释本研究中睡眠重叠综合征患者比单纯 OSA 患者糖尿病发病的概率显著升高。

尽管 OSA 与 COPD 在老年男性患者中发病率最高,但本研究结果显示重叠综合征与糖尿病的相关性在相对年轻患者和女性患者中尤其显著。虽然年轻患者和女性患者心血管疾病和代谢性疾病的发病风险相对较小,但是 OSA、COPD 或者二者兼而有之的重叠综合征给上述人群带来的疾病隐患更大,当然,他们也最可能成为从早期干预获益的人群。这种现象比较合理的推测是老年男性患者存在比较多的危险因素,复杂的病史增加了这些患者的临床风险,同时"稀释"了重叠综合征与糖尿病的相关

性,而年轻患者和女性患者的健康状况相对比较好,COPD 和 OSA 与代谢性疾病的关系体现得更加显著。

持续气道正压通气(continuous positive airway pressure, CPAP)是治疗 OSA 的主要手段,而考虑 COPD 患者存在低通气,采用双水平呼吸机既能改善肺通气,又能解除气道梗阻,因此是重叠综合征治疗的合理选择。尽管对于 CPAP 治疗是否能改善心血管疾病患者的预后还存在争议[11],但大部分研究认可 CPAP 治疗对血压和血糖代谢的益处[12-13]。今后的研究可以关注双水平呼吸机治疗是否能降低代谢异常发生的风险,甚至有利于糖尿病的控制并减少未来并发症。

本研究收集了数量较多的临床和睡眠医学资料,睡眠监测结果均由专业睡眠技师判读,结果较为客观。本研究最主要的缺陷在于回顾性研究只能提供相关性的结论,而不能推导出重叠综合征导致糖尿病发生,由于缺乏 COPD 的分级,无法实施更详细的亚组分析,同时,COPD 的诊断完全取决于临床医师,因此回顾性的研究可能漏诊部分 COPD 患者。

综上所述,本研究证实了合并 OSA 与 COPD 的睡眠重叠综合征与 2 型糖尿病的发生存在显著的相关性,尤其是年轻患者和女性患者,睡眠重叠综合征与糖尿病发病关系密切,因此,睡眠重叠综合征应该得到临床更多的重视,今后的研究应关注双水平呼吸机治疗是否能降低代谢性疾病发生的风险,甚至降低其所致心血管疾病的风险。

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