·临床研究·

重度阻塞性睡眠呼吸暂停低通气综合征夜间血压波动特点及其继发高血压病的相关因素

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【摘 要】 **目的** 探讨伴与不伴有高血压病的重度阻塞性睡眠呼吸暂停低通气综合征(OSAHS)患者血压波动的特点及相关影响因素。**方法** 纳入南京医科大学附属淮安第一医院呼吸科2016年8月至2017年12月重度OSAHS患者125例,根据是否合并高血压分为高血压组($n=64$)及血压正常组($n=61$)。行多导睡眠图(PSG)检测时,同步测量脉搏传导时间(PTT)以行连续的动态血压监测。仰卧位清醒状态下,通过袖带测量血压,达到连续3个稳定血压测量值后行血压定标,血压及脉搏变化融合于PSG中。以呼吸事件发生时收缩压最高值与最低值的差值作为呼吸暂停事件相关血压波动幅度(△BP);以每小时△BP>10 mmHg(1 mmHg=0.133 kPa)次数作为血压波动频率(血压指数)。为进一步分析微觉醒及缺氧对血压波动的影响,将所有受试者整夜的呼吸暂停事件进行分类:A类,呼吸暂停事件仅伴有缺氧;B类,呼吸暂停事件仅伴有微觉醒;C类,呼吸暂停事件同时伴有微觉醒及缺氧,比较三类不同呼吸事件引起的△BP。采用SPSS 16.0统计软件进行数据处理。高血压组及血压正常组各项参数比较采用独立样本t检验。三类呼吸暂停事件的比较(A类、B类、C类)采用卡方检验。考察变量之间的相互关系首先使用Pearson相关分析,再行逐步多元回归分析。**结果** 高血压组的睡眠呼吸紊乱指标明显高于血压正常组;与血压正常组相比,高血压组的△BP和血压指数明显增高[(15.4±4.5) *vs* (10.9±2.6) mmHg;(57.0±16.5) *vs* (22.7±12.0)次/h,均$P<0.001$]。分析整夜呼吸事件提示A类呼吸事件的△BP明显大于B类[高血压组:(15.4±4.9) *vs* (11.9±3.8) mm Hg;血压正常组:(10.6±3.1) *vs* (9.5±2.4) mm Hg,均$P<0.001$],而C类中的△BP明显高于A类及B类(均$P<0.001$)。回归分析表明,与其他睡眠呼吸紊乱指数相比,血压指数(清醒期:$r^2=0.454$, $P<0.001$;睡眠期:$r^2=0.470$, $P<0.001$)及脉搏血氧饱和度(SpO_2)<90%累计时间($r^2=0.051$, $P<0.001$;睡眠期:$r^2=0.073$, $P<0.001$)与血压平均水平更相关。**结论** 在重度OSAHS中,高血压病的发生与夜间血压变异性增高及缺氧时间密切相关;微觉醒及缺氧均可引起血压的急剧增高,而缺氧占有主导地位。

【关键词】 阻塞性睡眠呼吸暂停;高血压病;血压波动;缺氧;微觉醒
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Characteristics of nocturnal blood pressure variability and relative factors of secondary hypertension in the patients with severe obstructive sleep apnea hypopnea syndrome

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【**Abstract**】 **Objective** To investigate the features and relative factors of blood pressure variability (BPV) in patients suffering from severe obstructive sleep apnea hypopnea syndrome (OSAHS) with and without hypertension. **Methods** A total of 125 patients with severe OSAHS in our hospital from August 2016 to December 2017 were divided into hypertensive group ($n=64$) and normotensive group ($n=61$). Blood pressure (BP) was continuously monitored and measured *via* pulse transit time (PTT) during polysomnography (PSG) and calibrated when 3 consecutive stable supine cuff values were obtained with patients in a conscious state. Variations in BP and pulse were incorporated in PSG. The amplitude of BP fluctuation (ΔBP) was reflected by the difference between the peak and bottom values of post apneic SBP recorded during an obstructive respiratory event, and the number of ΔBP>10 mmHg (1 mmHg=0.133 kPa) per hour of sleep time was used as indicator for frequency of significant BP fluctuations (BP index). To explore the effects of arousal and hypoxia on BP fluctuations, nocturnal respiratory events were classified into three types: type A with only oxygen desaturation; type B with arousal but without oxygen desaturation; and type C with both arousal and oxygen desaturation. △BP was compared between 3

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types. SPSS statistics 16.0 was used for data analysis, and all data were expressed as mean ± standard deviation. The independent sample Student's t test was used for comparison between the groups and Chi-square test for comparison between the 3 types of apnea events. Pearson's correlation and then a stepwise multiple regression analysis were performed to investigate the relationships between variables. **Results** Compared with the normotensive group, the hypertensive group had more severe sleep-disordered breathing (SDB) and significant higher ΔBP [(15.4 ± 4.5) *vs* (10.9 ± 2.6) mmHg] and BP index [(57.0 ± 16.5) *vs* (22.7 ± 12.0) times/h] (P <0.001 in both). Analysis of the nocturnal respiratory events showed that ΔBP were remarkably greater following type A than type B in hypertensive group[(15.4 ± 4.9) *vs* (11.9 ± 3.8) mmHg] and normotensive group [(10.6 ± 3.1) *vs* (9.5 ± 2.4) mmHg] (P <0.001 in both), and that ΔBP following type C were significantly higher than both type A and type B. A stepwise multiple regression equation demonstrated that the mean level of BP had a higher correlation with BP index [awake interval: r^2 = 0.454, P <0.001; sleep interval: r^2 =0.470, P <0.001)] and the percentage of sleep time with pulse oxygen saturation (SpO_2) <90% (awake interval: r^2 = 0.051, P < 0.001; sleep interval: r^2 = 0.073, P < 0.001) than with other sleep disorder parameters. **Conclusion** In the patients with severe OSAHS, the occurrences of hypertension are closely associated with increased nocturnal blood pressure variability (BPV) and hypoxic duration and can be induced by both hypoxia and arousal, with hypoxia being a dominant factor.

【Key words】 obstructive sleep apnea syndrome; hypertension; blood pressure fluctuation; hypoxia; arousal

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阻塞性睡眠呼吸暂停低通气综合征(obstructive sleep apnea hypopnea syndrome,OSAHS)患者夜间反复出现上气道阻塞,可导致间歇性低氧、频繁的微觉醒、胸内压改变等,引起血压变异性的增加[1,2]。国内外研究表明血压变异性与靶器官损害密切相关,且独立于血压平均水平[3,4]。既往研究多采用传统24 h袖带测压法来评估OSAHS血压变异性。该间断测压法无法与多导睡眠图(polysomnography,PSG)同步检测,难以捕捉呼吸暂停事件引起的血压波动,同时还易诱导微觉醒的发生,而微觉醒可引起血压的急剧增高[5],导致检测结果可能存在一定的误差。本研究在行PSG检测时,同步使用基于脉搏传导时间(pulse transit time,PTT)的连续测量法,对伴与不伴有高血压病的重度OSAHS患者行连续的动态血压监测,进一步阐述该类患者血压波动特点及继发高血压病相关因素的探讨。

1 对象与方法

1.1 对象

2016年8月至2017年12月,从就诊于南京医科大学附属淮安第一医院呼吸科睡眠中心患者中筛选重度OSAHS患者[呼吸暂停低通气指数(apnea-hypopnea index,AHI) >30次/h]125例,其中男性101例,女性24例,年龄(69.9 ± 12.1)岁,其中合并高血压病患者64例,血压正常患者61例。OSAHS诊断标准参照美国睡眠医学学会指南[6];高血压病诊断标准参照美国高血压学会指南[7]。

排除标准:(1)3个月内曾患有急性心肌梗死、心力衰竭、严重心律失常或脑血管意外;(2)血压≥180/110 mmHg(1 mmHg = 0.133 kPa);(3)拒绝本研究患者。为了避免降压药对本研究的影响,对口服降压药患者给予停药,期间严密监测血压变化,如出现头晕,心慌或血压≥180/110 mmHg,即刻给予临床干预并终止研究。停药时间取决于药物的半衰期以及最后一次给药时间。

本研究征得所有研究对象知情同意,并获南京医科大学附属淮安市第一人民医院临床试验伦理学委员会批准,同时在美国临床试验中心注册(ID:NCT02876471)。

1.2 方法

一般资料包括年龄、身高、体质量指数(body mass index,BMI)、颈围、腰围、Epworth嗜睡量表(Epworth Sleeping Scale,ESS)及门诊血压测量。

1.2.1 睡眠参数检测 行整夜PSG监测,主要检测指标为AHI,微觉醒指数,氧减指数(oxygen desaturation index,ODI),最低脉搏血氧饱和度(pulse oxygen saturation,SpO_2),平均SpO_2,睡眠间SpO_2低于90%时间占总睡眠时间的百分比(TST90),记录所有通道,根据标准行人工分析。

1.2.2 血压检测及数据分析 血压的连续测量依赖于PTT测量,国内外研究证明PTT可较好地反应血压的动态变化[8,9]。仰卧位清醒状态下,通过袖带测量血压,达到连续3个稳定血压测量值后行血压定标,血压及脉搏变化融合于PSG中。使用"DOMINO"软件(version 27.0,Randersacker GmbH,德国)分析。取平卧位清醒状态下10 min血压平均值作为清醒期血压,取整夜睡眠状态下血压平均值作为睡眠期血压。以呼吸事件发生时收缩压最高值与最低值之间差值作为呼吸暂停事件相关血压波动幅度(△BP);以每小时△BP >10 mmHg次数作为血压指数。

为进一步分析微觉醒及缺氧对血压波动的影响,将所有受试者整夜的呼吸暂停事件进行分类:A类,呼吸暂停事件仅伴有缺氧;B类,呼吸暂停事件仅伴有微觉醒;C类,呼吸暂停事件同时伴有微觉醒及缺氧,比较三组不同呼吸事件引起的△BP。

1.3 统计学处理

采用SPSS 16.0统计软件进行数据处理和分析。计量资料以均数±标准差($\bar{x}\pm s$)表示。高血压组及血压正常组各项参数比较采用独立样本t检验。计数资料以例数(百分率)表示,三类呼吸暂停事件的比较(A类、B类、C类)采用卡方检验。考察变量之间的相互关系首先使用Pearson相关分析,再行逐步多元回归分析。以$P<0.05$为差异有统计学意义。

2 结 果

2.1 2组患者一般资料及PSG监测指标比较

2组患者年龄、睡眠时间及性别比例均无差异。高血压组BMI、ESS评分、AHI、ODI、微觉醒指数、TST90、呼吸紊乱时间及氧减时间明显高于血压正常组(均$P<0.001$);最低SpO_2及平均SpO_2均明显低于血压正常组(均$P<0.001$;表1)。

2.2 2组患者血压波动比较

高血压组血压波动幅度及波动频率明显大于血压正常组[(15.4±4.5) *vs* (10.9±2.6) mmHg,(57.0±16.5) *vs* (22.7±12.0)次/h,均$P<0.001$;表1]。A类呼吸事件的△BP明显大于B类[高血压组:(15.4±4.9) *vs* (11.9±3.8) mmHg;血压正常组:(10.6±3.1) *vs* (9.5±2.4) mmHg,均$P<0.001$],而C类△BP明显高于A类及B类(均$P<0.001$;图1)。

2.3 血压平均值与血压波动及睡眠紊乱参数相关性分析

相关性分析显示清醒期以及睡眠期血压与BMI、AHI、ODI、TST90、血压指数、微觉醒指数、呼吸紊乱时间及氧减时间均呈正相关;与最低SpO_2及平均SpO_2均呈负相关。进入回归方程后,仅血压指数(清醒期:$r^2=0.454$,$P<0.001$;睡眠期:$r^2=0.470$,$P<0.001$)及TST90(清醒期:$r^2=0.051$,$P<0.001$;睡眠期:$r^2=0.073$,$P<0.001$)与血压平均水平相关(表2)。

表1 2组患者一般资料、PSG参数及血压指标比较

Table 1 Comparison of baseline data, PSG parameters and BP indices between two groups

Item	Hypertensive group ($n=64$)	Normotensive group ($n=61$)	P value
Age(years, $\bar{x}\pm s$)	69.6±11.9	70.1±12.2	0.473
Female[n(%)]	11(17.1)	13(21.3)	0.560
Neck circumference(cm, $\bar{x}\pm s$)	41.2±4.0	38.5±3.9	<0.001
Waist circumference(cm, $\bar{x}\pm s$)	108.9±7.8	103.3±8.6	<0.001
BMI(kg/m^2, $\bar{x}\pm s$)	30.1±3.9	28.1±3.6	0.005
ESS (score, $\bar{x}\pm s$)	14.2±4.2	10.9±4.6	<0.001
Awake BP(mmHg, $\bar{x}\pm s$)	156.4±9.1	124.2±8.9	<0.001
Sleep BP(mmHg, $\bar{x}\pm s$)	156.0±10.5	121.5±9.0	<0.001
TST(h, $\bar{x}\pm s$)	6.4±0.9	6.1±0.9	0.099
AHI(events/h, $\bar{x}\pm s$)	77.4±13.6	52.8±14.9	<0.001
ODI(events/h, $\bar{x}\pm s$)	71.7±14.4	46.4±15.5	<0.001
TST90(%, $\bar{x}\pm s$)	41.9±20.5	15.8±15.0	<0.001
Min SpO_2(%, $\bar{x}\pm s$)	64.9±8.8	72.4±9.4	<0.001
Mean SpO_2(%, $\bar{x}\pm s$)	89.2±4.1	93.2±2.1	<0.001
Arousal index(events/h, $\bar{x}\pm s$)	45.3±16.3	26.4±13.8	<0.001
Mean △BP(mmHg, $\bar{x}\pm s$)	15.4±4.5	10.9±2.6	<0.001
BP index(events/h, $\bar{x}\pm s$)	57.0±16.5	22.7±12.0	<0.001
Desaturation duration(min, $\bar{x}\pm s$)	231.8±65.7	152.6±67.8	<0.001
Events length(min, $\bar{x}\pm s$)	239.0±65.2	153.2±63.0	<0.001

PSG: polysomnography; BP: blood pressure; BMI: body mass index; ESS: Epworth Sleeping Scale; Awake BP: mean systolic blood pressure taken by pluse transit time during 10-minute quiet wakefulness period before sleep onset; Sleep BP: average of the systolic blood pressure during sleep period; TST: total sleep time; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; TST90: percentage of sleep time with pulse oxygen saturation <90%; Min SpO_2: minimum pulse oxygen saturation during sleep; Mean SpO_2: mean pulse oxygen saturation during sleep; Mean △BP: the mean value of event-related systolic blood pressure elevations; BP index: the number of △BP>10 mmHg per hour of sleep time; desaturation duration: the total time of nocturnal hypoxia; events length: the duration of respiratory disturbance. 1 mmHg=0.133 kPa

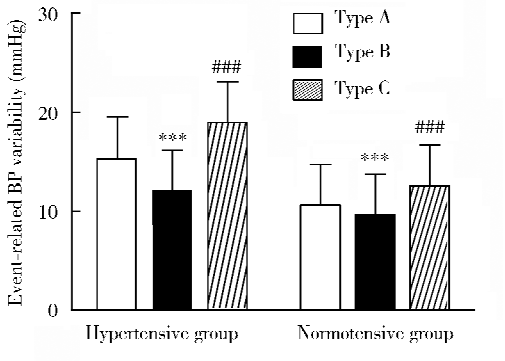


图1 2组患者不同呼吸事件相关的血压波动幅度比较

Figure 1 Comparison of apnea-related blood pressure variability caused by different types of events between two groups

Type A: apnea or hypopnea events end with oxygen desaturation only; Type B: only arousal takes place following apnea or hypopnea events; Type C: apnea or hypopnea events are accompanied with hypoxia and arousal. Compared with type A, $^{***}P<0.001$; compared with type A and B, $^{###}P<0.001$. 1 mmHg = 0.133 kPa

3 讨 论

本研究对重度 OSAHS 患者行连续的动态血压监测,且融合于 PSG 中,可准确地记录呼吸事件相关的血压波动。研究发现合并高血压病 OSAHS 患者的血压变异性明显大于单纯 OSAHS 患者,而频繁的血压波动可导致夜间、甚至白天血压平均水平增高。我们发现当呼吸事件发生更为密集时,两次呼吸暂停事件之间的血压保持在较高的水平,可能由于上次呼吸暂停事件发生时血压升高尚未恢复至正常血压水平,与下一次呼吸暂停事件引起的血压波动重叠,血压保持在较高水平基线上波动,促使夜间平均血压水平增高。而在清醒状态下,无缺氧发生,OSAHS 患者交感神经仍处于过度兴奋现象,可导致白天血压增高[10,11]。

微觉醒与缺氧均可引起血压波动,这与国内外研究结果相似[5,12],但关于两者对血压作用的强度存在争议。通过听觉刺激诱导健康受试者微觉醒的发生,微觉醒促发的血压波动幅度相当于 OSAHS 患者因呼吸事件引起的血压波动幅度的 75%[5]。另外,Yoon 等[12]研究也发现了微觉醒对血压波动的影响占有主导地位。而 O'Donnell 等[13]在狗的研究模型中发现呼吸暂停发生时的最低 SpO_2 与平均动脉压增高的幅度呈负相关,当 $SpO_2<80\%$ 时,相关性更明显。这提示缺氧越严重,对血压影响越大。本研究也证实了缺氧对血压波动的影响大于微觉醒,这可能与我们纳入的对象均为重度 OSAHS 患者且伴有严重缺氧有关。因此我们推断在呼吸暂停时间较短或低通气事件发生同时伴有轻度缺氧时,缺氧对血压波动的影响可能较小,这种情况下,微觉醒的作用可能大于缺氧,这可能是既往研究结果存在矛盾的原因。因此,在评估微觉醒以及缺氧对血压波动影响时,应考虑到患者的病情严重程度。另外,本研究亦发现,当呼吸事件同时伴有缺氧与微觉醒时对血压波动的影响大于上述的单一因素,两者存在协同作用。

相关性分析显示在重度 OSAHS 患者中,与 AHI 相比,血压平均水平与 TST90 更相关。目前仍以

表2 血压水平增高的相关危险因素分析

Table 2 Regression analysis of risk factors of blood pressure elevation

Item	Awake BP				Sleep BP			
	r	*P*	r^2	*P*	*r*	*P*	r^2	*P*
BP index	0.677	<0.001	0.454	<0.001	0.688	<0.001	0.470	<0.001
TST90	0.579	<0.001	0.051	<0.001	0.621	<0.001	0.073	<0.001
BMI	0.335	<0.001	…		0.362	<0.001	…	
ODI	0.557	<0.001	…		0.591	<0.001	…	
Min SpO_2	−0.373	<0.001	…		−0.423	<0.001	…	
Mean SpO_2	−0.500	<0.001	…		−0.547	<0.001	…	
AHI	0.558	<0.001	…		0.590	<0.001	…	
Arousal index	0.420	<0.001	…		0.451	<0.001	…	
Desaturation duration	0.481	<0.001	…		0.497	<0.001	…	
Events length	0.434	<0.001	…		0.440	<0.001	…	

Awake BP: mean systolic blood pressure taken by pulse transit time during 10-minute quiet wakefulness period before sleep onset; Sleep BP: average of the systolic blood pressure during sleep period; △BP: the value of event-related systolic blood pressure elevations; BP index: the number of △BP > 10 mmHg per hour of sleep time; TST90: percentage of sleep time with pulse oxygen saturation <90%; BMI: body mass index; ODI: oxygen desaturation index; Min SpO_2: minimum pulse oxygen saturation during sleep; Mean SpO_2: mean pulse oxygen saturation during sleep; AHI: apnea-hypopnea index; desaturation duration: the total time of nocturnal hypoxia; events length: the duration of respiratory disturbance

AHI来判断OSAHS病情严重程度，大量研究表明AHI与高血压发生密切相关[14,15]，然而在矫正了BMI、年龄等干扰因素后，两者的关系并非那么明显[16]。这提示单纯以AHI判断OSAHS的严重程度存在不足，因此，对重度OSAHS患者，预判其罹患心血管疾病风险时，我们更应重视其夜间整体缺氧水平。

总之，与单纯OSAHS相比，合并高血压病OSAHS患者呼吸紊乱程度严重，血压变异性较大，频繁的血压波动会导致夜间甚至白天继发性高血压病发生。另外，在重度OSAHS患者中，缺氧对血压波动及平均水平的影响大于微觉醒。

【参考文献】

[1] Martynowicz H, Porębska I, Poręba R, *et al*. Nocturnal blood pressure variability in patients with obstructive sleep apnea syndrome[J]. Adv Exp Med Biol, 2016, 952: 9-15. DOI: 10.1007/5584_2016_64.

[2] Leroy M, Van SC, Pilliere R, *et al*. Short-term variability of blood pressure during sleep in snorers with or without apnea[J]. Hypertension, 1996, 28(6): 937-943. DOI: 10.1161/01.hyp.28.6.937.

[3] Parati G, Pomidossi G, Albini F, *et al*. Relationship of 24-hour blood pressure mean and variability to severity of target-organ damage in hypertension[J]. J Hypertens, 1987, 5(1): 93. DOI: 10.1097/00004872-198702000-00013.

[4] Frattola A, Parati G, Cuspidi C, *et al*. Prognostic value of 24-hour blood pressure variability[J]. J Hypertens, 1993, 11(3): 1133-1137. DOI: 10.1097/00004872-199310000-00019.

[5] Davies RJ, Belt PJ, Roberts SJ, *et al*. Arterial blood pressure responses to graded transient arousal from sleep in normal humans[J]. J Appl Physiol, 1993, 74(3): 1123-1130. DOI: 10.1152/jappl.1993.74.1123-1130.

[6] Berry RB, Budhiraja R, Gottlieb DJ, *et al*. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine[J]. J Clin Sleep Med, 2012, 8(5): 597-619. DOI: 10.5664/jcsm.2172.

[7] Perloff D, Grim C, Flack J, *et al*. Human blood pressure determination by sphygmomanometry[J]. Circulation, 1993, 88(1): 2460-2470. DOI: 10.1161/01.CIR.88.5.2460.

[8] Vlahandonis A, Biggs SN, Nixon GM, *et al*. Pulse transit time as a surrogate measure of changes in systolic arterial pressure in children during sleep[J]. J Sleep Res, 2014, 23(4): 406-410. DOI: 10.1111/jsr.12140.

[9] Gao M, Olivier NB, Mukkamala R. Comparison of noninvasive pulse transit time estimates as markers of blood pressure using invasive pulse transit time measurements as a reference[J]. Physiol Rep, 2016, 4(10): e12768. DOI: 10.14814/phy2.12768.

[10] Somers VK, Dyken ME, Clary MP, *et al*. Sympathetic neural mechanisms in obstructive sleep apnea[J]. J Clin Invest, 1995, 96(4): 1897-1904. DOI: 10.1016/0895-7061(96)82092-9.

[11] Carlson JT, Hedner J, Elam M, *et al*. Augmented resting sympathetic activity in awake patients with obstructive sleep apnea[J]. Chest, 1993, 103(6): 1763-1768. DOI: 10.1378/chest.103.6.1763.

[12] Yoon IY, Jeong DU. Degree of arousal is most correlated with blood pressure reactivity during sleep in obstructive sleep apnea[J]. J Korean Med Sci, 2001, 16(6): 707-711. DOI: 10.3346/jkms.2001.16.707.

[13] O'Donnell CP, King ED, Schwartz AR, *et al*. Relationship between blood pressure and airway obstruction during sleep in the dog[J]. J Appl Physiol, 1994, 77: 1819-1828. DOI: 10.1152/jappl.1994.77(4)1819.

[14] Nieto FJ, Young TB, Lind BK, *et al*. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study[J]. JAMA, 2000, 283(14): 1829-1836. DOI: 10.1001/jama.283.14.1829.

[15] Peppard PE, Young T, Palta M, *et al*. Prospective study of the association between sleep-disordered breathing and hypertension[J]. N Engl J Med, 2000, 342(19): 1378-1384. DOI: 10.1056/nejm200005113421901.

[16] Cano-Pumarega I, Durán-cantolla J, Aizpuru F, *et al*. Obstructive sleep apnea and systemic hypertension: longitudinal study in the general population: the Vitoria Sleep Cohort[J]. Am J Respir Crit Care Med, 2011, 184(11): 1299-1304. DOI: 10.1164/rccm.201101-0130oc.

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