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SCIENTIFIC INVESTIGATIONS

Breathing rate variability in obstructive sleep apnea during wakefulness

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Study Objectives: Obstructive sleep apnea (OSA) is defined by pauses in breathing during sleep, but daytime breathing dysregulation may also be present. Sleep may unmask breathing instability in OSA that is usually masked by behavioral influences during wakefulness. A breath-hold (BH) challenge has been used to demonstrate breathing instability. One measure of breathing stability is breathing rate variability (BRV). We aimed to assess BRV during rest and in response to BH in OSA.

Methods: We studied 62 participants (31 with untreated OSA: respiratory event index [mean ± SD] 20 ± 15 events/h, 12 females, age 51 ± 14 years, body mass index [BMI] 32 ± 8 kg/m^2; 31 controls: 17 females, age 47 ± 13 years; BMI 26 ± 4 kg/m^2). Breathing movements were collected using a chest belt for 5 minutes of rest and during a BH protocol (60 seconds baseline, 30 seconds BH, 90 seconds recovery, 3 repeats). From the breathing movements, we calculated median breathing rate (BR) and interquartile BRV at rest. We calculated change in BRV during BH recovery from baseline. Group comparisons of OSA vs control were conducted using analysis of covariance with age, sex, and BMI as covariates.

Results: We found 10% higher BRV in OSA vs controls ($P < .05$) during rest. In response to BH, BRV increased 7% in OSA vs 1% in controls ($P < .001$). Resting BR was not significantly different in OSA and controls, and sex and age did not have any significant interaction effects. BMI was associated with BR at rest ($P < .05$) and change in BRV with BH ($P < .001$), but no significant BMI-by-group interaction effect was observed.

Conclusions: The findings suggest breathing instability as reflected by BRV is high in OSA during wakefulness, both at rest and in response to a stimulus. Breathing instability together with high blood pressure variability in OSA may reflect a compromised cardiorespiratory consequence in OSA during wakefulness.

Keywords: sleep-disordered breathing, breath-hold, loop gain, respiration, lung

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Patients with obstructive sleep apnea show altered wakefulness physiology, which may contribute to poor health outcomes. We assessed 1 aspect of daytime breathing regulation, breathing instability, as measured with breathing rate variability in participants with obstructive sleep apnea vs healthy participants.

Study Impact: We found higher breathing rate variability in obstructive sleep apnea compared with controls during rest and in response to a breath-hold challenge. The findings reflect breathing instability in obstructive sleep apnea, which may be linked to impaired cardiovascular control.

INTRODUCTION

Obstructive sleep apnea (OSA) is defined by pauses in breathing (apneas) during sleep, but during wakefulness, physiology is also affected.[1] One potential OSA pathophysiology is elevated pharyngeal dilator muscle activity, which is thought to be a compensatory mechanism during wakefulness, but at sleep onset, loss in pharyngeal dilator muscular activity could allow upper airway collapse in those patients who are anatomically susceptible.[2–4] Another example of altered awake physiological processes in OSA is high chemoreflex activity, which may be adaptive during sleep but which might also affect breathing regulation during wakefulness.[2,5] Furthermore, given the coupling between cardiac and respiratory systems,[6] breathing patterns during wakefulness may be influenced by the high variability in resting blood pressure (BP) in OSA, as we previously reported.[7] This variability may reflect a reduced ability to maintain homeostasis in terms of matching perfusion with metabolic demand and gas exchange.[8,9] Indeed, although variability is a fundamental biological property, it was reported over 50 years ago that altered rhythm, particularly a reduction in heart rate variability (likely leading to higher BP variability) is associated with poor prognosis.[10] More recently, variability in respiratory rate has also been shown to be a biomarker of an individual's pathophysiological state.[11–17]

At rest, the maintenance of adequate oxygen supply to body tissues such as the heart and brain is regulated by baroreceptor and chemoreceptor reflexes that control BP and respiration, respectively. Fluctuations in BP and blood oxygen, carbon dioxide, and pH are buffered by these 2 reflexes, and reduced stability of these important homeostatic mechanisms is reflected in greater variability of respiratory and cardiovascular parameters. In OSA, altered cardiovascular function is reflected in higher autonomic tone as measured by muscle sympathetic nerve activity,[18,19] diminished heart rate responses to autonomic challenges,[20] and higher moment-to-moment BP variability.[7]

Short-term fluctuating BP waves, called Traube waves, are associated with slower breathing and apneas.[21] In addition to resting variability, the functioning of these homeostatic mechanisms can be assessed during challenges that disturb an individual's physiologic state, forcing these mechanisms to adapt. For example, a breath-hold (BH) for approximately 30 seconds is one such challenge that alters blood chemistry, producing a decrease in arterial blood flow and oxygenation, and the subsequent recovery from this event has been used to assess loop gain indirectly in OSA.[22]

In OSA, waking breathing instability is expected given blood-gas exchange problems,[23] altered function in brain areas responsible for breathing control,[24,25] and breathing muscle weakness.[26] Additionally, in some patients, there appears to be excess soft tissue in the upper airway that affects airflow as reflected in a saw-tooth pattern in spirometer flowgraphs.[12] However, this saw-tooth pattern is influenced by smoking and obesity and is not a strong predictor of OSA.[11–13] Malfunctioning peripheral chemoreceptors and high reactivity of the ventilatory system can lead to unstable respiratory control referred to as high loop gain—that is, the propensity of a system governed by feedback loops to develop unstable behavior.[27] High loop gain is observed in many patients with OSA.[28,29] While loop gain is not a readily available measure, breathing instability may instead be reflected as variations in breathing rate (BR). Variability in awake BR reflects variations in timing of inspiration and expiration, which, in turn, can be influenced by breath depth as well as pauses immediately after expiration and immediately prior to the next inspiration.[30] Since BR is derived from breathing or airflow movements, it can be measured from a simple sensor such as a respiratory belt and is therefore a readily available measure of breathing instability that could be assessed in OSA.[31]

The objective of the present study was to determine if there was breathing instability in OSA as reflected by high BR variability. We aimed to assess BR variability at rest and following a BH challenge. Several factors may influence breathing patterns. First, sex differences are apparent in clinical and physiological aspects of OSA,[32–34] so we expect breathing instability in OSA to differ with sex. Second, age can be a potential confounder, especially in women, since premenopausal women may have different BP regulation than postmenopausal women and the former may be less impacted by intermittent hypoxia.[35,36] Third, obesity is associated with both OSA and hypoventilation syndrome[37–39] and relative lung volume is lower in obese individuals.[40] We hypothesized that people with OSA would have increased BR variability (BRV) during wake, independent of other influences of sex, age, and body mass index (BMI).

METHODS

We studied 31 untreated participants with OSA and 31 control participants, which was a convenience sample size based on recruitment over a set time period, with the numbers matched in the control and OSA groups. Recruitment was through the local community via printed and electronic flyers. All participants underwent a 3-step screening for potential sleep-disordered breathing or other sleep disorders. During enrollment, a phone screening included questions about diagnosed sleep disorders, sleep complaints, mental health disorders, or snoring. After initial enrollment, participants completed a questionnaire about medical history, sleep disorders, sleep complaints, menopausal status, and daytime sleepiness (Epworth Sleepiness Scale [ESS]). All diagnoses of OSA were performed through the UCLA Sleep Disorders Center. Some of the participants who were placed in the OSA group had OSA recently diagnosed (< 6 months), so the sleep study was not repeated. Those participants who received an OSA diagnosis more than 6 months prior performed a new sleep study. Other participants with suspected OSA were also studied. Sleep studies consisted of 2-night home sleep apnea testing with an "ARES" device.[41] The ARES has electrodes in the FP1 and FP2 positions for deriving electroencephalogram, electrooculogram, and electromyogram, although the measurements derived from this device do not qualify for the American Academy of Sleep Medicine (AASM) definition of home sleep apnea testing sleep vs wake, and a respiratory event index (REI) is derived as opposed to the gold-standard apnea-hypopnea index. The ARES device captures airflow using a nasal cannula and pressure transducer, and an apnea is derived by a cessation (> 90% reduction) in flow for ≥ 10 seconds, and a hypopnea ≥ 50% reduction in flow for ≥ 10 seconds. The criteria for REI apneas and hypopneas are a minimum of 4% desaturation, consistent with the 2012 AASM scoring criteria.[42] The scoring assigned to participants was based on the average over the single night with the longest valid recording time. Diagnostic criteria for OSA included an REI ≥ 5 events/h and the presence of at least 1 other daytime symptom.[43] All participants with OSA were not using continuous positive airway pressure (CPAP) or any other treatment for their sleep disorder. Participants were placed into the control group who did not report any sleep disorders or suspected symptoms during the 3-step screening process. Potential control participants who did report daytime sleepiness (ESS ≥ 11) or other sleep complaints (n = 12) were given the home sleep apnea test to ensure they did not have OSA or any other sleep disorder. In these 12 participants, the mean ± SD REI was 0.5 ± 0.8 events/h, minimum oxygen saturation was 89% ± 6%, and average oxygen saturation was 96% ± 2%.

Exclusion criteria for all participants included the following: other sleep disorders; major illness or head injury; stroke; major cardiovascular disease; current tobacco use; recent (< 3 months) use of psychotropic treatment, including medications; recent use of cardiovascular medications with major autonomic influences, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers; and diagnosed mental health disorder other than anxiety or unipolar depressive conditions. All procedures were approved by the UCLA Institutional Review Board. All participants provided written informed consent. **Table 1** shows clinical and demographic details.

Procedures were performed at UCLA. Participants were asked to avoid caffeine or other stimulants 24 hours beforehand and to avoid eating before their visit if possible or limit their

Table 1—Participant characteristics.

	All			Females			Males		
	Control (n = 31)	OSA (n = 31)	*P*	Control (n = 17)	OSA (n = 12)	*P*	Control (n = 14)	OSA (n = 19)	*P*
Age (y)	47.2 ± 12.7	51.6 ± 14.4	*.04**	48.2 ± 11.1	56.6 ± 13.6	*.00**	45.9 ± 14.7	48.4 ± 14.3	.58
	[23.0–67.0]	[25.0–77.0]		[34.0–66.0]	[34.0–77.0]		[23.0–67.0]	[25.0–77.0]	
BMI (kg/m^2)	26.1 ± 4.3	32.5 ± 7.8	*.00**	25.8 ± 5.1	32.7 ± 9.3	*.01**	26.5 ± 3.1	32.3 ± 6.9	*.01**
	[19.8–37.6]	[21.9–54.3]		[19.8–37.6]	[21.9–54.3]		[21.8–32.7]	[22.2–46.3]	
BR at rest (bpm)	16.2 ± 3.7	15.6 ± 3.7	.38	15.6 ± 4.3	14.9 ± 3.2	.47	16.8 ± 2.7	16.0 ± 4.1	.53
	[6.1–23.3]	[6.6–23.2]		[6.1–20.5]	[6.6–18.8]		[12.5–23.3]	[7.4–23.2]	
BRV at rest (bpm)	3.9 ± 1.3	5.3 ± 2.9	*.00**	3.9 ± 1.2	4.6 ± 2.1	.27	3.8 ± 1.5	5.7 ± 3.3	*.04**
	[1.5–7.2]	[1.9–16.2]		[1.5–5.8]	[2.9–9.8]		[2.0–7.2]	[1.9–16.2]	
Relative % BRV at rest	26.2 ± 14.4	36.1 ± 22.9	*.03**	28.8 ± 7.3	33.6 ± 19.3	.47	23.1 ± 9.6	37.7 ± 25.2	*.04**
	[9.2–67.5]	[13.3–124.7]		[9.2–67.5]	[15.3–72.2]		[14.3–47.5]	[13.3–124.7]	
Change in BRV at BH recovery from baseline (bpm)	0.1 ± 0.7	0.9 ± 2.3	*.03**	0.1 ± 0.8	1.1 ± 1.4	*.01**	0.1 ± 0.6	0.8 ± 2.8	.14
	[−2.0 to 1.9]	[−4.5 to 6.4]		[−2.0 to 1.9]	[−0.7 to 3.5]		[−1.3 to 0.7]	[−4.5 to 6.4]	
Percentage change of BRV during BH recovery relative to BR at rest	1.1 ± 6.2	7.0 ± 22.0	.08	1.7 ± 8.0	9.7 ± 15.0	.06	0.4 ± 3.3	5.3 ± 25.6	.17
	[−10.4 to 28.7]	[−57.8 to 68.7]		[−10.4 to 28.7]	[−4.7 to 49.7]		[−7.4 to 4.5]	[−57.8 to 68.7]	
Sleep parameters									
REI (events/h)	n/a	20.4 ± 15.4	n/a	n/a	24.7 ± 21.3	n/a	n/a	17.6 ± 10.0	n/a
		[6.0–67.4]			[6.9–67.4]			[6.0–42.0]	
SaO_2 (minimum %)	n/a	83.6 ± 6.0	n/a	n/a	83.3 ± 6.5	n/a	n/a	83.7 ± 5.6	n/a
		[68.8–92.0]			[70.9–92.0]			[68.8–92.0]	
SaO_2 (baseline %)	n/a	94.8 ± 1.5	n/a	n/a	94.8 ± 1.4	n/a	n/a	94.8 ± 1.6	n/a
		[91.0–96.5]			[92.0–96.5]			[91.0–96.4]	

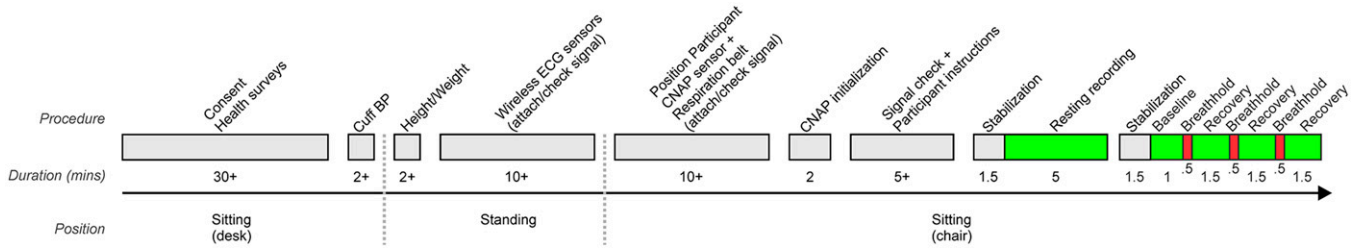
Demographic and physiological measures are shown. Values are means ± SDs [range] for participants with OSA and control participants, with separation by sex. * $P \leq .05$. Independent-samples *t* test *P* values for OSA vs controls are shown (italicized if ≤ .05). BH = breath-hold, BMI = body mass index, bpm = breaths per minute, BR = breathing rate, BRV = breathing rate variability, n/a = not applicable, OSA = obstructive sleep apnea, REI = respiratory event index, SaO_2 = blood oxygen saturation, SD = standard deviation.

food intake to a light meal. Visits were scheduled midmorning (9:30 AM earliest) to early evening (6:30 PM latest start). After consenting, we measured participants' height and weight for BMI calculation and recorded resting blood pressure (Omron 3 series BP monitor; Omron, Kyoto, Japan.). At the start of the visit, we collected participant demographics and medical history, including menopausal status in women, using online surveys completed in a private room.

Recordings were made in a quiet room, with participants seated in a comfortable but upright position, with arms resting on armrests. After initial signal quality checking, participants were instructed to sit quietly and look at a screen. A research team member was in the same room. The rest protocol consisted of a 5-minute seated resting physiologic data-collection period, subsequent to a 90-second stabilization period. The BH protocol involved 3 identical challenges. After 60 seconds of baseline stabilization, participants were instructed to BH for 30 seconds followed by 90 seconds of recovery, repeated 3 times (**Figure 1**). Instructions were to wait for a visual and auditory cue, then to exhale, then inhale fully, then hold until a second cue 30 seconds later. The 30-second duration has been commonly used for decades,[44] and even though Messineo et al[22] used 20 seconds, we have found that all participants with OSA regardless of age and health could achieve the longer duration. We selected a 90-second stabilization period as being long enough to allow breathing to return to and remain at baseline, as supported by the 40-second post-BH recovery observed by Messineo et al.[22] We selected 3 repeats as a balance between participant engagement and statistical power.

Resting physiological data were collected with BIOPAC's MP150 system with AcqKnowledge 5.0 software (BIOPAC Systems Inc, Goleta, CA). We obtained breathing movements from a respiration belt. The respiration signal through BIOPAC was sampled at 250 Hz, and bandpass filtered at 60 Hz (**Figure 2**). We used AcqKnowledge 5.0 to identify inspiration and expiration start times, with verification by trained experts (**Figure 2**). We created a rate channel in the program to visually identify any spurious signals. We exported the times of the end inspiration/start expiration peaks as beats per minute to Excel (Microsoft Corporation, Redmond, WA) and calculated

Figure 1—Protocol timeline.



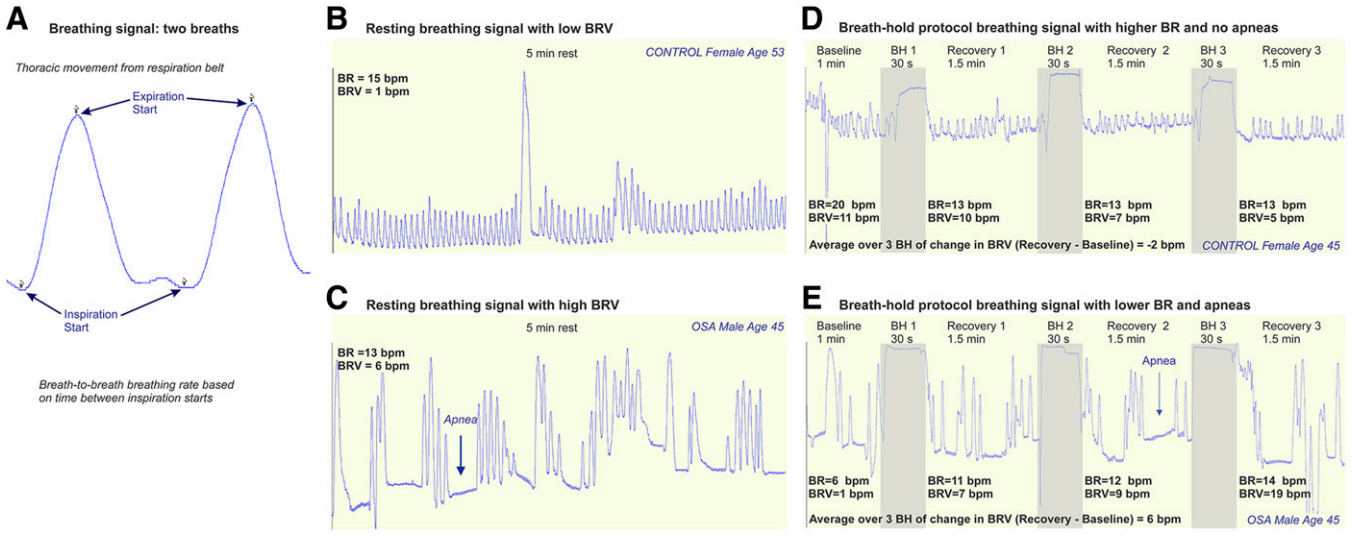
Sequence, participant position, and duration of procedures. Colored areas show which data were used for analysis, with green indicating rest or baseline and recovery from breath-hold (in red). Participants had back support in the "Chair" but not the "Desk." BP = blood pressure, CNAP = continuous noninvasive arterial pressure, ECG = electrocardiogram.

the median BR and interquartile range of the BRV for the resting-state data (**Figure 2**). Other measures for the BH included the relative change in BRV from rest, and the delta change in BRV during the BH recovery compared with baseline, averaged over the 3 tasks (**Figure 2**). We utilized IBM SPSS version 27 (IBM Corporation, Armonk, NY) to conduct 3 separate analyses of covariance (ANCOVA) tests on BR at rest, BRV at rest, and the change in BRV at BH recovery from baseline. In each ANCOVA, we compared OSA vs control with age, sex, and BMI as covariates. We also investigated group-by-covariate interaction effects if we found a significant main effect of the covariate. Effect sizes for these models were reported as partial η^2. We correlated significant covariates with respiratory variables, including BR, BRV change during BH recovery, and BRV during rest.

RESULTS

Participant characteristics and descriptive statistics are shown in **Table 1**, and ANCOVA results are shown in **Table 2**. The mean ± SD ESS scores were 5 ± 3 in controls and 8 ± 3 in participants with OSA. In women, menopausal status was more postmenopausal in OSA and more premenopausal in controls (postmenopausal: 50% OSA vs 25% controls; perimenopausal: 8% OSA vs 10% controls; premenopausal: 42% OSA vs 65% controls). We observed pauses in breathing in OSA but not control participants' breathing signals. The ANCOVA model revealed that at rest, participants with OSA displayed significantly greater BRV compared with controls (OSA mean ± SD breaths per minute [bpm]: 5.3 ± 2.9; control: 3.9 ± 1.3; $P < .05$).

Figure 2—Sample traces illustrating BR calculation and different degrees of BRV during rest and BH.



(A) Breathing signal from thoracic movements recorded by respiration belt over 2 breaths, with inspiration and expiration transitions detected using AcqKnowledge 5.0 with manual verification; BR was calculated from expiration starts (peaks). **(B)** Breathing signal during 5 minutes of rest with a low BRV. **(C)** Breathing signal during 5 minutes of rest with a high BRV. The small oscillations during the apnea are due to cardiac movement. **(D, E)** Breathing signals with BR and BRV values for baseline and recoveries for the 3 BH instances. BH = breath-hold, bpm = breaths per minute, BR = breathing rate, BRV = breathing rate variability, OSA = obstructive sleep apnea.

Table 2—ANCOVA results.

	Group	Covariates		
	OSA vs Control	Sex	Age	BMI
Model 1: rest BR	0.02 (P = .1)	0.03 (P = .23)	0.00 (P = .7)	0.03* (P = .04)
Model 2: rest BRV	0.04* (P = .02)	0.015 (P = .3)	0.01 (P = .4)	0.02 (P = .3)
Model 3: change in BRV with BH	0.1* (P = .0005)	0.005 (P = .7)	0.005 (P = .6)	0.1* (P = .0003)

Data presented as partial η^2 (P values). Normalized effect sizes and P values of ANCOVA for the 3 dependent variables. Effect sizes for ANCOVA are partial η^2; by convention, effect size categories are ≤ 0.01 small, 0.02–0.06 medium, and > 0.06 large. *P ≤ .05. ANCOVA = analysis of covariance, BMI = body mass index, BR = breathing rate, BRV = breathing rate variability, OSA = obstructive sleep apnea.

In addition, following the BH challenge, the OSA group displayed a significantly increased delta change in BRV at BH recovery (OSA: 0.9 ± 2.3; control: 0.1 ± 0.7; $P < .001$). In relative terms, BRV was 10% higher in OSA compared with controls, and in response to BH, there was a 7% increase over baseline in BRV in OSA vs a 1% increase in the control group. In contrast, at rest, BR in OSA was not significantly reduced compared with controls (OSA mean ± SD bpm: 15.6 ± 3.7; control: 16.2 ± 3.7; $P = .1$). Group means of breathing variables are illustrated in **Figure 3**.

The ANCOVA model confirmed that the group effects remained after accounting for covariates of age, sex, and BMI. The ANCOVA model showed a higher BRV during rest in OSA vs controls ($P < .05$, effect of group) and an increase in BRV with BH in OSA vs controls ($P < .001$, effect of group). BR was not significantly different in OSA and controls during rest accounting for other factors. Sex and age did not have any significant interaction effects, but BMI showed significant interaction effects for an increase in BRV with BH ($P < .001$) and BR at rest ($P < .05$). The standardized effect sizes are shown in **Table 2**. Since BMI had significant interaction effects in the ANCOVA model, we assessed associations with other variables. **Table 3** shows the correlations of BMI with each of the 3 dependent variables of rest BR, rest BRV, and change in BRV at BH recovery from baseline. In OSA, BMI was negatively correlated both with BRV at rest (Pearson's R: OSA: −.36, $P = .04$; control: −.09, $P = .63$) and with the BRV increases during BH recovery (OSA: −.51, $P = .003$; control: −.18, $P = .33$). BMI was positively correlated with BR in OSA but not the control group (OSA: .36, $P = .04$; control: .10, $P = .51$).

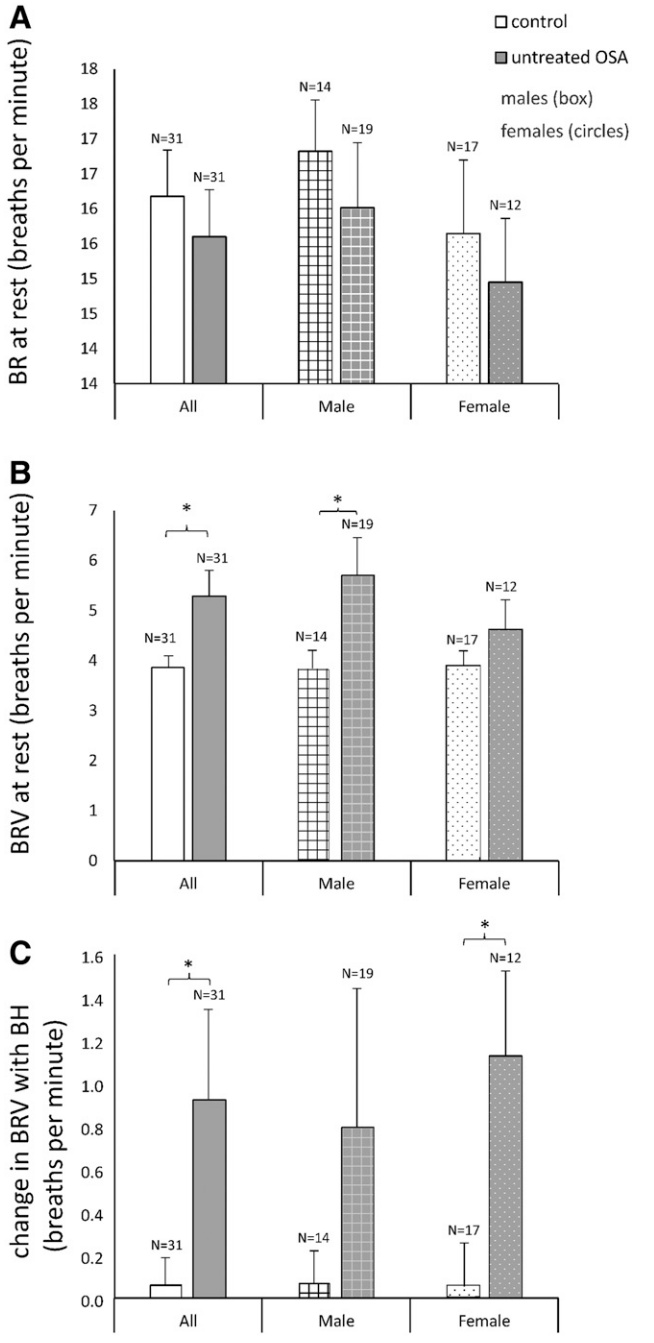
DISCUSSION

At rest during wakefulness, we found increased BRV in participants with untreated OSA compared with healthy individuals. Similarly, a BH challenge elicited an increase in BRV during recovery from baseline in participants with OSA compared with controls. Since ventilation demands are relatively stable at rest, the high resting BRV is presumably a reflection of disrupted breathing control in OSA during wakefulness.[2] Spontaneous breathing in the absence of common or external stimuli adapts to regulate ventilation based on neural control involving the brainstem rhythm generator, signals from chemoreceptors, and respiratory muscle effectors.[46,47] Considering the earlier findings of disrupted chemo-sensation during wakefulness,[48,49] the present findings suggest some combination of altered chemosensory processing and respiratory muscle control or function results in unstable breathing in OSA.

A higher BRV reflects some combination of longer or shorter breaths relative to a lower BRV. In OSA, the higher BRV relative to control coincides with a trend to lower BR, suggesting a greater incidence of longer breaths. High BRV may reflect a tendency of people with OSA to have periodic waxing and waning of breathing, akin to periodic breathing during sleep, as seen in both OSA and central sleep apnea, and conditions such as heart failure,[50–52] with the latter also showing variations during wakefulness.[53] Periodicity in breathing and breathing instability in sleep disorders is attributed to disrupted chemoreflexes.[27] However, in healthy awake people, spontaneous periodic breathing has been observed with hypoxic exercise,[54] and sleep at altitude is frequently accompanied by periodic breathing,[55] both conditions that involve a disruption of the levels of arterial partial pressure of carbon dioxide ($PaCO_2$) and oxygen saturation. Consequently, the patterns seen in patients with OSA at rest likely reflect a disruption of a combination of the levels of blood gas carbon dioxide and oxygen, the time for chemoreceptor signals to be processed and result in ventilatory muscle activation or relaxation, and the gain of the chemoreceptor responses. At rest, the role of central command is minimal.

Breathing instability could be reflected in characteristics not captured by BR. For example, the ratio of inspiration time to total breath time (duty cycle) may be altered in OSA.[56–59] A difference in relative durations of inspiration and expiration rate where participants with OSA have difficulty in exhaling carbon dioxide fully before the start of the next breath[60] will increase the duty cycle, although how this might affect variability in BR is unclear. Duty cycle independent of BR can reflect compensation for inspiratory airflow limitation during sleep in OSA.[57] During wakefulness, OSA is associated with impaired neurological control of the upper airway dilator muscle,[11,13] with perhaps protective reflexes that increase dilator muscle activity to

Figure 3—Dependent variable group comparisons.



Bar graphs with mean and SD of breathing variables in breaths per minute (bpm). **(A)** Mean BR over 5 minutes' rest. **(B)** BRV measured as SD of BR over 5 minutes' rest. **(C)** Average over three 30-second BH challenges of change in BRV, calculated as difference from 30-second baseline (immediately prior to BH) to 30-second recovery (immediately after BH). Significant differences between groups indicated by *$P \leq .05$ BH = breath-hold, BR = breathing rate, BRV = breathing rate variability, OSA = obstructive sleep apnea, SD = standard deviation.

maintain airway patency.[26,58,59] To compensate for this increased activity, a change in the duty cycle rather than breathing rate may be present with wakefulness with OSA.[56]

Respiration is modulated by sympathetic activity,[61] and changes in breathing may be adaptive for controlling BP fluctuations to help maintain homeostasis as regulated by the baroreflex circuit.[19] However, the influence could also be in the other direction, with breathing influencing BP.[62] The respiratory sinus arrhythmia is an association between breathing and cardiac output most likely based on the baroreflex responses to changes in intrathoracic pressure with expansion and contraction of the lungs.[63,64] Sympathetic activation affects circulation, which could impact blood-gas exchange and hence chemosensory drive in OSA.[26,65] Thus, the cardiorespiratory interactions that differ in people with OSA are likely associated with the increased sympathetic activity observed in the sleep disorder, relative to healthy people.[62,66]

The coupling between respiratory rhythm and sympathetic outflow likely results as a consequence of crosstalk between various brainstem circuits. Since pontomedullary transection in experimental animals significantly reduces respiratory modulation of sympathetic drive, the areas responsible for this integration likely lie in the pons or medulla.[67] Indeed, it has been reported that untreated OSA is associated with increased gray matter volumes and significantly reduced sympathetic nerve activity–related functional magnetic resonance imaging signal changes in the brainstem, more specifically in the dorsolateral pons, rostral ventrolateral medulla, and medullary raphe.[68] It was noted that these anatomical and functional changes in the dorsolateral pons encompassed the region of the parabrachial and Kölliker-Fuse nuclei. It is known from experimental animal studies that chemical stimulation of this region can evoke increases or decreases in arterial pressure and sympathetic nerve activity.[69–71] Furthermore, the lateral parabrachial and Kölliker-Fuse nuclei are important for respiratory control as they contain neurons that are critical for respiratory rhythm and the transition between inspiration and expiration.[72–74]

Importantly, it was recently shown in an experimental animal preparation that during vagal nerve stimulation, inhibiting the Kölliker-Fuse nucleus enhanced respiratory rhythm entrainment and reduced rhythm variability. It was suggested that these properties are consistent with that of a high-gain model, and it was concluded that the Kölliker-Fuse "regulates respiratory rhythm variability via a gain control mechanism."[75] Altered activity within this brainstem region in OSA would almost certainly affect respiratory rhythm and may underlie the respiratory patterns reported here. Critically, the pontine structural and sympathetic-mediated activity neural changes reported in untreated patients with OSA were completely reversed by 6–12 months of CPAP treatment.[76,77] Given this, if the changes in respiratory function in OSA result from neural changes in areas such as the Kölliker-Fuse nucleus, one would predict that restoration of neural function by CPAP treatment would reverse the respiratory changes reported here.

Obesity may confound the breathing patterns observed here. Obesity is known to be correlated with saw-tooth respiratory pattern in OSA.[11] We found that BMI correlated with an increasing BR and decreasing BRV and lower change in BRV at the following BH. Previous studies show that obese patients have higher respiratory rates than nonobese controls, and with

Table 3—Correlation of BMI with respiration variables.

	BMI Correlation		
	Rest BR	Rest BRV	Change in BRV with BH
OSA (n = 31)	*R* = *.36* (*P* = *.04*)	*R* = *−.37* (*P* = *.04*)	*R* = *−.51* (*P* = *.003*)
Control (n = 31)	*R* = .10 (*P* = .51)	*R* = −.09 (*P* = .63)	*R* = −.18 (*P* = .33)

BMI correlations with BR, BRV at rest, and change in BRV at BH recovery from baseline are represented by the Pearson's *R* correlation coefficients in each of the untreated OSA and control groups. The significance level was set at *P* < .05. Significant Pearson's *R* correlation coefficients are italicized. BH = breath-hold, BMI = body mass index, BR = breathing rate, BRV = breathing rate variability, OSA = obstructive sleep apnea.

fat deposits reducing the flexibility of the trunk and reducing breathing flexibility,[78,79] which may lead to reduced BRV as observed here in obese participants. Since BMI is a major risk factor for OSA, the interaction of weight and OSA may influence the present findings. Specifically, since the OSA group has a higher BMI than controls, the pattern of lower BRV with higher BMI would go counter to the higher BRV with OSA. Hence, if BMI is not accounted for, it would lead to a lower reported effect size of OSA on BRV.

Limitations

We did not observe statistically significant effects for sex or age. However, relative to the control group, a higher percentage of women with OSA were postmenopausal, which is consistent with OSA epidemiology, and which theoretically could impact the findings.[80] In larger studies, women compared with men showed a higher thoracic-to-abdominal contribution, whereas increasing age was associated with reduced rib cage contributions to tidal volume and compensatory increases in abdominal movements.[81] These factors could explain the nonsignificant but higher by 1 bpm breathing rate in the seated position observed in those studies in women vs men.[81] We expect sex differences in breathing patterns would emerge with larger samples of patients with OSA, but the potential magnitudes of such effects are unclear. We expect age and sex differences in breathing patterns would emerge with larger samples of patients with OSA[(82–83)], but the potential magnitudes of such effects are unclear. We also expect that age and menopausal influences would be present in larger samples, given the progressive nature of OSA.[84–86]

Another limitation of the study is that it is possible that the simple window technique (30-second block) of measuring BRV following BH blurs moment-to-moment changes, so more detailed analyses of time to return to baseline levels may be more sensitive to OSA influences. Behavioral influences may have shifted the breathing from purely physiology-driven patterns. Our protocol was designed to provide a consistent experience leading up to the 5 minutes' recording, including both procedures and verbal instructions (**Figure 1**), but we anecdotally observed variation in participant experiences, including reports of the rest period being restful, boring, or stressful. Such variations would likely lead to greater individual variability, but it is also possible that there are consistent behavioral influences that differ between OSA and controls, especially give our recent finding of above-normal stress levels in the sleep disorder.[87]

CONCLUSIONS

We found a pattern of higher BRV indicating higher breathing instability in patients with OSA compared with healthy participants during wakefulness. Similarly, a higher BRV was elicited by a 30-second BH challenge in patients with OSA, whereas BRV in healthy participants returned to baseline levels immediately after the same BH challenge. BRV is tightly linked with cardiovascular patterns, including BP, through respiratory and autonomic neural circuitry. Such neural circuitry is impacted by OSA, and altered neural function may contribute to the instability of cardiorespiratory physiology observed in OSA. Future studies could assess whether BRV covaries with BPV in OSA. Since CPAP resolves some neural dysfunction in OSA, another question is whether CPAP treatment also normalizes some cardiorespiratory physiology during wakefulness. More generally, this study found that BRV is a potentially informative marker of a physiological state specific to people with OSA.

ABBREVIATIONS

ANCOVA, analysis of covariance
BMI, body mass index
BP, blood pressure
bpm, breaths per minute
BPV, mean arterial blood pressure variability
BR, median breathing rate
BRV, breathing rate variability
CPAP, continuous positive airway pressure
ESS, Epworth Sleepiness Scale
OSA, obstructive sleep apnea
REI, respiratory event index

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