Title
Breathing rate variability in obstructive sleep apnea during wakefulness.

Journal
Journal of Clinical Sleep Medicine, 18(3)

ISSN
1550-9389

Authors
Pal, Amrita
Martinez, Fernando
Akey, Margaret A
et al.

Publication Date
2022-03-01

DOI
10.5664/jcsm.9728

Peer reviewed

Breathing rate variability in obstructive sleep apnea during wakefulness

Amrita Pal, PhD [1], Fernando Martinez, BS[1], Margaret A. Akey[1], Ravi S. Aysola, MD, [2], Luke A. Henderson, PhD[3], Atul Malhotra, MD[4], Paul M. Macey, PhD [1,*]

[1]UCLA School of Nursing, [2]Division of Pulmonary and Critical Care, David Geffen School of Medicine at UCLA, University of California, Los Angeles, California, United States of America;

[3]Brain and Mind Centre, School of Medical Sciences, University of Sydney, Sydney, Australia;

[4]Department of Pulmonary Critical Care & Sleep Medicine, University of California, San Diego, California, United States of America.

* Correspondence to:
Paul M. Macey
UCLA School of Nursing
700 Tiverton Ave
Los Angeles, CA 90095-1702
USA
Phone/voicemail: +1-424-234-3244
Email: pmacey@ucla.edu

Research activities were performed at the University of California, Los Angeles, USA.

All authors have seen and approved the manuscript.

The authors report no financial disclosures.

The investigation does not involve off-label or investigational use of any intervention.

The authors report no conflicts of interest.

The manuscript does not report results of a clinical trial.

Number of tables: 3

Number of figures: 3

Abstract word count: 292

Brief summary word count: 82

Manuscript word count: 3695

Abstract

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 earlier 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 untreated OSA: Respiratory Event Index (REI) [mean±s.d.] 20±15 events/hour, 12 females, age 51±14years, BMI 32±8kg/m^2; 31 control: 17 females, age 47±13; BMI 26±4). Breathing movements were collected using a chest belt for 5 minutes rest and during a BH protocol (60 s baseline, 30 s BH, 90 s 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 (ANCOVA) with age, sex and BMI as covariates.

Results. We found 10% higher BRV in OSA vs. control (p<0.05) during rest. In response to BH, BRV increased 7% in OSA vs. 1% in controls (p<0.001). Resting BR was not significantly different in OSA and control, and sex and age did not have any significant interaction effects. BMI was associated with BR at rest (p<0.05) and change in BRV with BH (p<0.001), 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

Brief summary

a. **Current knowledge/ Study rationale:** Patients with obstructive sleep apnea (OSA) show altered wakefulness physiology, which may contribute to poor health outcomes. We assessed one aspect of daytime breathing regulation, breathing instability, as measured with breathing rate variability (BRV) in OSA versus healthy participants.

b. **Study impact:** We found higher BRV in OSA compared to control during rest and in response to a breath-hold challenge. The findings reflect breathing instability in OSA, 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 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 of 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 [14-17].

At rest, the maintenance of adequate oxygen supply to body tissues such as the heart and brain is regulated by baroreceptor and chemoreceptor reflexes which control blood pressure (BP) and respiration, respectively. Fluctuations in blood pressure and blood oxygen, carbon dioxide and pH are buffered by these two 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 saw-tooth pattern in spirometer flow graphs [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]. Whilst 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.

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. Firstly, sex differences are apparent in clinical and physiological aspects of OSA [32-34], so we expect breathing instability in OSA to differ with sex. Secondly, 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]. Thirdly, 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.

Methods

We studied 31 untreated 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 fliers. All participants underwent a three-step screening for potential sleep disordered breathing or other sleep disorders. During enrolment, a phone screening included questions about diagnosed sleep disorders, sleep complaints, mental health disorders, or snoring. After initial enrolment, 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 that 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 consistent of two-night home sleep apnea testing (HSAT) with an "ARES" device [41]. The ARES has electrodes in FP1 and FP2 positions for deriving electroencephalogram (EEG), electrooculogram (EOG) and electromyogram (EMG), although the measurements derived from this device do not qualify for the AASM definition of HSAT sleep vs wake, and a respiratory event index (REI) is derived as opposed to the gold-standard apnea-hypopnea index (AHI). 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/h and the presence of at least one other daytime symptom [43]. All OSA participants 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 three-step screening process. Potential control participants who did report daytime sleepiness, ESS ≥ 11, or other sleep complaints (n=12) were given the HSAT to ensure they did not have OSA or any other sleep disorder. In these 12 participants, the REI mean±s.d. was 0.5±0.8 events/hr, minimum oxygen saturation was 89±6% and average oxygen saturation was 96±2%.

Exclusion criteria for all participants included 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, 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 food intake to a light meal. Visits were scheduled mid-morning (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, 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 (s) stabilization period. The breath-hold (BH) protocol involved three identical challenges. After 60 s of baseline stabilization, participants were instructed to BH for 30 s followed by 90 s of recovery, repeated three 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 s later. The 30 s duration has been commonly used for decades [44] and even though Messineo et al. used 20 s [22], we have found that all OSA participants regardless of age and health could achieve the longer duration. We selected a 90 s stabilization period as being long enough to allow breathing to return to and remain at baseline, as supported by the 40 s post-BH recovery observed by Messineo et al. [22]. We selected three 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, USA). 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 and calculated the median breathing rate (BR) and interquartile range of the breathing rate (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 to baseline, averaged over the three tasks (Figure 2). We measured height and weight at the time of the visit, and calculated BMI. Participants completed an online survey of demographics and medical history. Descriptive statistics were calculated in Excel. We utilized IBM SPSS v27 to conduct three separate analysis 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 versus control with age, gender 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 eta squared. 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 in Table 2. The mean±s.d. Epworth Sleepiness Scale (ESS) scores were 5±3 in control and 8±3 in OSA. In women, menopausal status was more postmenopausal in OSA and more premenopausal in control (postmenopausal: 50% OSA vs. 25% control; perimenopausal: 8% OSA vs. 10% control; premenopausal: 42% OSA vs. 65% control). We observed pauses in breathing in OSA but not control participants' breathing signals. The ANCOVA model revealed that at rest, OSA participants displayed significantly greater BRV compared with controls (OSA mean±s.d. bpm: 5.3±2.9, control 3.9±1.3; $p<0.05$). In addition, following the BH challenge, the OSA group displayed significantly increased delta change of

BRV at BH recovery (OSA 0.9±2.3, control 0.1±0.7; $p<0.001$). 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 versus a 1% increase in the control group. In contrast, at rest, BR in OSA was not significantly reduced compared with controls (OSA mean±s.d. bpm: 15.6±3.7, control 16.2±3.7; $p=0.1$). Group means of breathing variables are illustrated in Figure 3.

The ANCOVA model confirmed 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. control ($p<0.05$ effect of group), and increase in BRV with BH in OSA vs. control ($p<0.001$, effect of group). BR was not significantly different in OSA and control during rest accounting for other factors. Sex and age did not have any significant interaction effects, but BMI showed significant interaction effects for increase in BRV with BH ($p<0.001$) and BR at rest ($p<0.05$). The standardized effect sizes are 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 three 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 -0.36, $p=0.04$; control -0.09, $p=0.63$) and with the BRV increases during BH recovery (OSA -0.51, $p=0.003$; control -0.18, $p=0.33$). BMI was positively correlated with BR in OSA but the control group (OSA 0.36 $p=0.04$; control 0.10, $p=0.51$).

Discussion

At rest during wakefulness, we found increased BRV in participants with untreated OSA compared to healthy individuals. Similarly, a BH challenge elicited an increase in BRV during recovery from baseline in participants with OSA compared to controls. Since at rest ventilation demands are relatively stable, the high resting BRV is presumably a reflection of disrupted breathing control in OSA during wakefulness [2,31]. 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 $PaCO_2$, and O_2 saturation. Consequently, the patterns seen in OSA patients at rest likely reflect a disruption of a combination of the levels of blood gas CO_2 and O_2, the time for chemoreceptors 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 breathing rate. For example, the ratio of inspiration time to total breath time (duty cycle) may be altered in OSA [56]. A difference in relative durations of inspiration and expiration rate where the OSA participants 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 of breathing rate is unclear. Duty cycle independent of breathing rate 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 maintain airway patency [5826,59]. 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 one 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 cardio-respiratory 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 cross-talk 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 grey 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 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 sawtooth respiratory pattern in OSA[11]. We found that BMI correlated with an increasing BR, and decreasing BRV and lower change in BRV at following BH. Previous studies show obese patients have higher respiratory rates than non-obese controls, and with 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 control, 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 OSA women were postmenopausal, which is consistent with OSA epidemiology, and which theoretically could impact the findings [80]. In larger studies, women compared to men show higher thoracic to abdominal contribution, whereas increasing age was associated with reduced rib cage contributions to tidal volume and compensatory increases in abdomen movements [81]. These factors could explain the non-significant but higher by 1 bpm breathing rate in the seating position observed in those studies in women vs. men [81]. We expect sex differences in breathing patterns would emerge with larger samples of OSA patients, 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 subject-to-subject variability, but it is also possible that there are consistent behavioral influences that differ between OSA and control, especially give our recent finding of above-normal stress levels in the sleep disorder [87].

Conclusion

We found a pattern of higher BRV indicating higher breathing instability in OSA patients compared with healthy participants during wakefulness. Similarly, higher BRV was elicited by a 30 s BH challenge in OSA patients, 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 BRV is a potentially informative marker of a physiological state specific to people with OSA.

Abbreviations

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
CVD	cardiovascular disorders
ESS	Epworth Sleepiness Scale
HSAT	home sleep apnea testing
MSNA	muscle sympathetic nerve activity
OSA	obstructive sleep apnea
REI	respiratory event index
s	seconds

Acknowledgements

This research was supported by the National Institute of Nursing Research NR-017435, National Institute of Heart, Lung and Blood Institute HL-135562. We thank Jaimi N. Shepperd, and Andrea P. Aguila for assisting with the physiology set up and data collection. We would like to acknowledge Roopsha Chatterjee in the data entry and physiological data artifact-correction process. We would like to thank Dr. Mary-Lynn Brecht from UCLA School of Nursing for providing statistical support.

References

1. Jayaraj R, Mohan J, Kanagasabai A. A Review on Detection and Treatment Methods of Sleep Apnea. J Clin Diagn Res. 2017; 11 (3): Ve01-ve03.
2. Malhotra A, Deacon N, Powell F, Katz ES. Adaptive responses using obstructive sleep apnea as the paradigm. Physiology (Bethesda, Md). 2014; 29 (3): 153-155.
3. Khoo MC, Marmarelis VZ. Estimation of peripheral chemoreflex gain from spontaneous sigh responses. Ann Biomed Eng. 1989; 17 (6): 557-570.
4. Younes M, Ostrowski M, Thompson W, Leslie C, Shewchuk W. Chemical control stability in patients with obstructive sleep apnea. Am J Respir Crit Care Med. 2001; 163 (5): 1181-1190.
5. Nava-Guerra L, Edwards BA, Terrill PI, et al. Quantifying ventilatory control stability from spontaneous sigh responses during sleep: a comparison of two approaches. Physiol Meas. 2018; 39 (11): 114005.
6. Pitzalis MV, Mastropasqua F, Massari F, et al. Effect of respiratory rate on the relationships between RR interval and systolic blood pressure fluctuations: a frequency-dependent phenomenon. Cardiovascular Research. 1998; 38 (2): 332-339.
7. Pal A, Martinez F, Aguila AP, et al. Beat-to-beat blood pressure variability in patients with obstructive sleep apnea. J Clin Sleep Med. 2021; 17 (3): 381-392.
8. Guardiola J, Yu J, Hasan N, Fletcher EC. Evening and morning blood gases in patients with obstructive sleep apnea. Sleep Med. 2004; 5 (5): 489-493.
9. Pittman R. The Circulatory System and Oxygen Transport. In. *Regulation of Tissue Oxygenation*. San Rafael, CA: Morgan & Claypool Life Sciences; 2011.
10. Hon EH, Lee ST. Electronic Evaluation of the Fetal Heart Rate. Viii. Patterns Preceding Fetal Death, Further Observations. Am J Obstet Gynecol. 1963; 87: 814-826.
11. Sanders MH, Martin RJ, Pennock BE, Rogers RM. The Detection of Sleep Apnea in the Awake Patient: The 'Saw-Tooth' Sign. JAMA. 1981; 245 (23): 2414-2418.
12. Bourne MH, Jr., Scanlon PD, Schroeder DR, Olson EJ. The sawtooth sign is predictive of obstructive sleep apnea. Sleep Breath. 2017; 21 (2): 469-474.
13. Vincken W, Cosio MG. Flow oscillations on the flow-volume loop: a nonspecific indicator of upper airway dysfunction. Bull Eur Physiopathol Respir. 1985; 21 (6): 559-567.
14. Brack T, Jubran A, Tobin MJ. Dyspnea and decreased variability of breathing in patients with restrictive lung disease. Am J Respir Crit Care Med. 2002; 165 (9): 1260-1264.
15. Bien MY, Hseu SS, Yien HW, et al. Breathing pattern variability: a weaning predictor in postoperative patients recovering from systemic inflammatory response syndrome. Intensive Care Med. 2004; 30 (2): 241-247.
16. Papaioannou VE, Chouvarda IG, Maglaveras NK, Pneumatikos IA. Study of multiparameter respiratory pattern complexity in surgical critically ill patients during weaning trials. BMC Physiol. 2011; 11: 2.
17. White CE, Batchinsky AI, Necsoiu C, et al. Lower interbreath interval complexity is associated with extubation failure in mechanically ventilated patients during spontaneous breathing trials. J Trauma. 2010; 68 (6): 1310-1316.
18. Ueno-Pardi LM, Guerra RS, Goya TT, et al. Muscle Metaboreflex Control of Sympathetic Activity in Obstructive Sleep Apnea. Med Sci Sports Exerc. 2017; 49 (7): 1424-1431.
19. Narkiewicz K, Borne PJHvd, Montano N, Dyken ME, Phillips BG, Somers VK. Contribution of Tonic Chemoreflex Activation to Sympathetic Activity and Blood Pressure in Patients With Obstructive Sleep Apnea. Circulation. 1998; 97 (10): 943-945.

20. Macey PM, Kumar R, Woo MA, Yan-Go FL, Harper RM. Heart rate responses to autonomic challenges in obstructive sleep apnea. PLoS One. 2013; 8 (10): e76631.
21. DORNHORST AC, HOWARD P, LEATHART GL. Respiratory Variations in Blood Pressure. Circulation. 1952; 6 (4): 553-558.
22. Messineo L, Taranto-Montemurro L, Azarbarzin A, et al. Breath-holding as a means to estimate the loop gain contribution to obstructive sleep apnoea. J Physiol. 2018; 596 (17): 4043-4056.
23. Jensen MLF, Vestergaard MB, Tønnesen P, Larsson HBW, Jennum PJ. Cerebral blood flow, oxygen metabolism, and lactate during hypoxia in patients with obstructive sleep apnea. Sleep. 2018; 41 (3).
24. Harper RM, Kumar R, Macey PM, Woo MA, Ogren JA. Affective brain areas and sleep-disordered breathing. Prog Brain Res. 2014; 209: 275-293.
25. Park B, Palomares JA, Woo MA, et al. Disrupted functional brain network organization in patients with obstructive sleep apnea. Brain Behav. 2016; 6 (3): e00441.
26. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. Physiological reviews. 2010; 90 (1): 47-112.
27. Randerath W, Deleanu OC, Schiza S, Pepin J-L. Central sleep apnoea and periodic breathing in heart failure: prognostic significance and treatment options. European Respiratory Review. 2019; 28 (153): 190084.
28. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. Am J Respir Crit Care Med. 2013; 188 (8): 996-1004.
29. Deacon NL, Catcheside PG. The role of high loop gain induced by intermittent hypoxia in the pathophysiology of obstructive sleep apnoea. Sleep Med Rev. 2015; 22: 3-14.
30. Zamoscik VE, Schmidt SNL, Gerchen MF, et al. Respiration pattern variability and related default mode network connectivity are altered in remitted depression. Psychological Medicine. 2018; 48 (14): 2364-2374.
31. Rolfe S. The importance of respiratory rate monitoring. British Journal of Nursing. 2019; 28 (8): 504-508.
32. Macey PM, Kumar R, Yan-Go FL, Woo MA, Harper RM. Sex differences in white matter alterations accompanying obstructive sleep apnea. Sleep. 2012; 35 (12): 1603-1613.
33. Macey PM, Prasad JP, Ogren JA, et al. Sex-specific hippocampus volume changes in obstructive sleep apnea. NeuroImage Clinical. 2018; 20: 305-317.
34. Macey PM, Rieken NS, Ogren JA, Macey KE, Kumar R, Harper RM. Sex differences in insular cortex gyri responses to a brief static handgrip challenge. Biology of sex differences. 2017; 8: 13-13.
35. Hinojosa-Laborde C, Mifflin Steven W. Sex Differences in Blood Pressure Response to Intermittent Hypoxia in Rats. Hypertension. 2005; 46 (4): 1016-1021.
36. Mauvais-Jarvis F, Clegg DJ, Hevener AL. The role of estrogens in control of energy balance and glucose homeostasis. Endocr Rev. 2013; 34 (3): 309-338.
37. Al Dabal L, Bahammam AS. Obesity hypoventilation syndrome. Annals of thoracic medicine. 2009; 4 (2): 41-49.
38. Porhomayon J, Papadakos P, Singh A, Nader ND. Alteration in respiratory physiology in obesity for anesthesia-critical care physician. HSR proceedings in intensive care & cardiovascular anesthesia. 2011; 3 (2): 109-118.
39. Jehan S, Zizi F, Pandi-Perumal SR, et al. Obstructive Sleep Apnea and Obesity: Implications for Public Health. Sleep Med Disord. 2017; 1 (4): 00019.
40. Jones RL, Nzekwu MM. The effects of body mass index on lung volumes. Chest. 2006; 130 (3): 827-833.
41. Ayappa I, Norman RG, Seelall V, Rapoport DM. Validation of a self-applied unattended monitor for sleep disordered breathing. Journal of Clinical Sleep Medicine. 2008; 4 (01): 26-37.

42. Berry RB, Purdy S, Kantner G, et al. 0463 Validation of a Home Sleep Apnea Testing Device for the Diagnosis of Sleep Disordered Breathing based on AASM 2012 guidelines. Sleep. 2019; 42 (Supplement_1): A186-A186.
43. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep. 1999; 22 (5): 667-689.
44. Hasegawa M, Kern EB. The effect of breath holding, hyperventilation, and exercise on nasal resistance. Rhinology. 1978; 16 (4): 243-249.
45. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods. 2007; 39 (2): 175-191.
46. Blain GM, Smith CA, Henderson KS, Dempsey JA. Peripheral chemoreceptors determine the respiratory sensitivity of central chemoreceptors to CO(2). J Physiol. 2010; 588 (Pt 13): 2455-2471.
47. Gray PA, Rekling JC, Bocchiaro CM, Feldman JL. Modulation of respiratory frequency by peptidergic input to rhythmogenic neurons in the preBotzinger complex. Science. 1999; 286 (5444): 1566-1568.
48. Hedner JA, Wilcox I, Laks L, Grunstein RR, Sullivan CE. A specific and potent pressor effect of hypoxia in patients with sleep apnea. Am Rev Respir Dis. 1992; 146 (5 Pt 1): 1240-1245.
49. Mansukhani MP, Kara T, Caples SM, Somers VK. Chemoreflexes, sleep apnea, and sympathetic dysregulation. Curr Hypertens Rep. 2014; 16 (9): 476.
50. Sands SA, Edwards BA, Kee K, et al. Control theory prediction of resolved Cheyne-Stokes respiration in heart failure. Eur Respir J. 2016; 48 (5): 1351-1359.
51. AlDabal L, BaHammam AS. Cheyne-Stokes Respiration in Patients with Heart Failure. Lung. 2010; 188 (1): 5-14.
52. Brown HW, Plum F. The neurologic basis of Cheyne-Stokes respiration. The American Journal of Medicine. 1961; 30 (6): 849-860.
53. Pinna GD, Maestri R, Mortara A, La Rovere MT. Cardiorespiratory interactions during periodic breathing in awake chronic heart failure patients. Am J Physiol Heart Circ Physiol. 2000; 278 (3): H932-941.
54. Hermand E, Pichon A, Lhuissier FJ, Richalet JP. Periodic breathing in healthy humans at exercise in hypoxia. J Appl Physiol (1985). 2015; 118 (1): 115-123.
55. Ainslie PN, Lucas SJ, Burgess KR. Breathing and sleep at high altitude. Respir Physiol Neurobiol. 2013; 188 (3): 233-256.
56. Lo Y-L, Jordan AS, Malhotra A, et al. Influence of wakefulness on pharyngeal airway muscle activity. Thorax. 2007; 62 (9): 799-805.
57. Schneider H, Krishnan V, Pichard LE, Patil SP, Smith PL, Schwartz AR. Inspiratory duty cycle responses to flow limitation predict nocturnal hypoventilation. Eur Respir J. 2009; 33 (5): 1068-1076.
58. Eckert DJ, Malhotra A. Pathophysiology of adult obstructive sleep apnea. Proc Am Thorac Soc. 2008; 5 (2): 144-153.
59. Mezzanotte WS, Tangel DJ, White DP. Waking genioglossal electromyogram in sleep apnea patients versus normal controls (a neuromuscular compensatory mechanism). J Clin Invest. 1992; 89 (5): 1571-1579.
60. Rapoport DM, Garay SM, Epstein H, Goldring RM. Hypercapnia in the Obstructive Sleep Apnea Syndrome: A Reevaluation of the “Pickwickian Syndrome”. Chest. 1986; 89 (5): 627-635.
61. Fatouleh R, Macefield VG. Cardiorespiratory coupling of sympathetic outflow in humans: a comparison of respiratory and cardiac modulation of sympathetic nerve activity to skin and muscle. Exp Physiol. 2013; 98 (9): 1327-1336.
62. Nuckowska MK, Gruszecki M, Kot J, et al. Impact of slow breathing on the blood pressure and subarachnoid space width oscillations in humans. Scientific Reports. 2019; 9 (1): 6232.

63. Piepoli M, Sleight P, Leuzzi S, et al. Origin of respiratory sinus arrhythmia in conscious humans. An important role for arterial carotid baroreceptors. Circulation. 1997; 95 (7): 1813-1821.
64. Slovut DP, Wenstrom JC, Moeckel RB, Wilson RF, Osborn JW, Abrams JH. Respiratory sinus dysrhythmia persists in transplanted human hearts following autonomic blockade. Clin Exp Pharmacol Physiol. 1998; 25 (5): 322-330.
65. Lusina SJ, Kennedy PM, Inglis JT, McKenzie DC, Ayas NT, Sheel AW. Long-term intermittent hypoxia increases sympathetic activity and chemosensitivity during acute hypoxia in humans. J Physiol. 2006; 575 (Pt 3): 961-970.
66. Lombardi C, Pengo MF, Parati G. Obstructive sleep apnea syndrome and autonomic dysfunction. Autonomic Neuroscience. 2019; 221: 102563.
67. Baekey DM, Dick TE, Paton JF. Ponto-medullary transection attenuates sympathorespiratory coupling and eliminates cardiac sinus arrhythmia in the in situ rat. The FASEB Journal. 2008; 22 (S1): 739.736-739.736.
68. Lundblad LC, Fatouleh RH, Hammam E, McKenzie DK, Macefield VG, Henderson LA. Brainstem changes associated with increased muscle sympathetic drive in obstructive sleep apnoea. Neuroimage. 2014; 103: 258-266.
69. Dampney RA. Functional organization of central pathways regulating the cardiovascular system. Physiol Rev. 1994; 74 (2): 323-364.
70. Hade JS, Mifflin SW, Donta TS, Felder RB. Stimulation of parabrachial neurons elicits a sympathetically mediated pressor response in cats. Am J Physiol. 1988; 255 (6 Pt 2): H1349-1358.
71. Miyawaki T, Kawamura H, Komatsu K, Yasugi T. Chemical stimulation of the locus coeruleus: inhibitory effects on hemodynamics and renal sympathetic nerve activity. Brain Res. 1991; 568 (1-2): 101-108.
72. Nuding SC, Segers LS, Baekey DM, et al. Pontine-ventral respiratory column interactions through raphe circuits detected using multi-array spike train recordings. J Neurophysiol. 2009; 101 (6): 2943-2960.
73. Rybak IA, O'Connor R, Ross A, et al. Reconfiguration of the pontomedullary respiratory network: a computational modeling study with coordinated in vivo experiments. J Neurophysiol. 2008; 100 (4): 1770-1799.
74. Segers LS, Nuding SC, Dick TE, et al. Functional connectivity in the pontomedullary respiratory network. J Neurophysiol. 2008; 100 (4): 1749-1769.
75. Dhingra RR, Dutschmann M, Galan RF, Dick TE. Kolliker-Fuse nuclei regulate respiratory rhythm variability via a gain-control mechanism. Am J Physiol Regul Integr Comp Physiol. 2017; 312 (2): R172-R188.
76. Lundblad LC, Fatouleh RH, McKenzie DK, Macefield VG, Henderson LA. Brain stem activity changes associated with restored sympathetic drive following CPAP treatment in OSA subjects: a longitudinal investigation. J Neurophysiol. 2015; 114 (2): 893-901.
77. Henderson LA, Fatouleh RH, Lundblad LC, McKenzie DK, Macefield VG. Effects of 12 Months Continuous Positive Airway Pressure on Sympathetic Activity Related Brainstem Function and Structure in Obstructive Sleep Apnea. Front Neurosci. 2016; 10: 90.
78. LITTLETON SW. Impact of obesity on respiratory function. Respirology. 2012; 17 (1): 43-49.
79. Power JD, Lynch CJ, Silver BM, Dubin MJ, Martin A, Jones RM. Distinctions among real and apparent respiratory motions in human fMRI data. NeuroImage. 2019; 201: 116041.
80. Jehan S, Auguste E, Zizi F, et al. Obstructive Sleep Apnea: Women's Perspective. Journal of sleep medicine and disorders. 2016; 3 (6): 1064.
81. Mendes LPDS, Vieira DSR, Gabriel LS, et al. Influence of posture, sex, and age on breathing pattern and chest wall motion in healthy subjects. Braz J Phys Ther. 2020; 24 (3): 240-248.
82. Reuter S, Moser C, Baack M. Respiratory distress in the newborn. Pediatr Rev. 2014; 35 (10): 417-429.

83. Sinnreich R, Kark JD, Friedlander Y, Sapoznikov D, Luria MH. Five minute recordings of heart rate variability for population studies: repeatability and age-sex characteristics. Heart. 1998; 80 (2): 156-162.
84. Tsuji H, Larson MG, Venditti FJ, Jr., et al. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation. 1996; 94 (11): 2850-2855.
85. Garpestad E, Katayama H, Parker JA, et al. Stroke volume and cardiac output decrease at termination of obstructive apneas. J Appl Physiol (1985). 1992; 73 (5): 1743-1748.
86. Marrone O, Riccobono L, Salvaggio A, Mirabella A, Bonanno A, Bonsignore MR. Catecholamines and blood pressure in obstructive sleep apnea syndrome. Chest. 1993; 103 (3): 722-727.
87. Wong JL, Martinez F, Aguila AP, et al. Stress in obstructive sleep apnea. Sci Rep. 2021; 11 (1): 12631.

Figure Legends.

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 "Desk". BP = blood pressure; CNAP = continuous non-invasive arterial pressure; ECG = electrocardiogram.

Figure 2. Sample traces illustrating breathing rate calculation, and different degrees of breathing rate variability during rest and breath hold.

A. Breathing signal from thoracic movements recorded by respiration belt over two 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, and **C.** breathing signal during 5 minutes of rest with a high BRV. The small oscillations during the apnea are due to cardiac movement. **D and E.** Breathing signals with BR and BRV values for baseline and recoveries for the three breath-hold (BH) instances.

Figure 3. Dependent variable group comparisons.

Bar graphs with mean and s.d. of breathing variables in breaths per minute (bpm). **A.** Mean breathing rate (BR) over 5 minutes' rest, **B.** BR variability (BRV) measured as standard deviation of BR over 5 minutes' rest, **C.** Average over three 30 s breath hold (BH) challenges of change in BRV, calculated as difference from 30 s baseline (immediately prior to HB) to 30 s recovery (immediately after BH). Significant differences between groups indicated by * ($p \leq 0.05$) or ** ($p \leq 0.001$).

Tables

Table 1: Participant characteristics

Demographic and physiological measures. Mean ± stdev [Range] of for OSA and control participants, with separation by sex. Independent samples t-test p values for OSA vs. control are shown (italicized if ≤ 0.05). BH: breath hold; BMI: body mass index; bpm: breaths per minute; BR: breathing rate; BRV: BR variability; REI: respiratory event index; SaO_2: blood oxygen saturation.

	All			Females			Males		
	CONTROL Mean ± std [Range] N = 31	OSA Mean ± std [Range] N = 31	t-test *p*-values	CONTROL Mean ± std [Range] N = 17	OSA Mean ± std [Range] N = 12	t-test *p*-values	CONTROL Mean ± std [Range] N = 14	OSA Mean ± std [Range] N = 19	t-test *p*-values
Age (years)	47.2 ± 12.7 [23.0–67.0]	51.6 ± 14.4 [25.0–77.0]	*0.04*	48.2 ± 11.1 [34.0–66.0]	56.6 ± 13.6 [34.0–77.0]	*0.00*	45.9 ± 14.7 [23.0–67.0]	48.4 ± 14.3 [25.0-77.0]	0.58
BMI (m^2/kg)	26.1 ± 4.3 [19.8–37.6]	32.5 ± 7.8 [21.9-54.3]	*0.00*	25.8 ± 5.1 [19.8–37.6]	32.7 ± 9.3 [21.9–54.3]	*0.01*	26.5 ± 3.1 [21.8–32.7]	32.3 ± 6.9 [22.2-46.3]	*0.01*
BR at rest (bpm)	16.2 ± 3.7 [6.1–23.3]	15.6 ± 3.7 [6.6–23.2]	0.38	15.6 ± 4.3 [6.1–20.5]	14.9 ± 3.2 [6.6–18.8]	0.47	16.8 ± 2.7 [12.5–23.3]	16.0 ± 4.1 [7.4–23.2]	0.53
BRV at rest(bpm)	3.9 ± 1.3 [1.5–7.2]	5.3 ± 2.9 [1.9–16.2]	*0.00*	3.9 ± 1.2 [1.5–5.8]	4.6 ± 2.1 [2.9–9.8]	0.27	3.8 ± 1.5 [2.0–7.2]	5.7 ± 3.3 [1.9–16.2]	*0.04*
Relative % BRV at rest	26.2 ± 14.4 [9.2–67.5]	36.1 ± 22.9 [13.3–124.7]	*0.03*	28.8 ± 7.3 [9.2–67.5]	33.6 ± 19.3 [15.3–72.2]	0.47	23.1 ± 9.6 [14.3–47.5]	37.7 ± 25.2 [13.3–124.7]	*0.04*
Change in BRV at BH recovery from baseline (bpm)	0.1 ± 0.7 [-2.0–1.9]	0.9 ± 2.3 [-4.5–6.4]	*0.03*	0.1 ± 0.8 [-2.0–1.9]	1.1 ± 1.4 [-0.7–3.5]	*0.01*	0.1 ± 0.6 [-1.3–0.7]	0.8 ± 2.8 [-4.5–6.4]	0.14
% change of BRV during BH recovery relative to BR at rest	1.1 ± 6.2 [-10.4–28.7]	7.0 ± 22.0 [-57.8–68.7]	0.08	1.7 ± 8.0 [-10.4–28.7]	9.7 ± 15.0 [-4.7–49.7]	0.06	0.4 ± 3.3 [-7.4–4.5]	5.3 ± 25.6 [-57.8–68.7]	0.17
Sleep parameters									
REI (events/hour)	n/a	20.4 ± 15.4 [6.0–67.4]	n/a	n/a	24.7 ± 21.3 [6.9–67.4]	n/a	n/a	17.6 ± 10.0 [6.0–42.0]	n/a
SaO_2 (minimum%)	n/a	83.6 ± 6.0 [68.8–92.0]	n/a	n/a	83.3 ± 6.5 [70.9–92.0]	n/a	n/a	83.7 ± 5.6 [68.8–92.0]	n/a
SaO_2 (baseline%)	n/a	94.8 ± 1.5 [91.0–96.5]	n/a	n/a	94.8 ± 1.4 [92.0–96.5]	n/a	n/a	94.8 ± 1.6 [91.0–96.4]	n/a

Table 2. ANCOVA results

*Normalized effect sizes and p-values of ANCOVA for the three dependent variables. Effect sizes for ANCOVA are partial eta-squared; by convention effect size categories are ≤ 0.01 small, 0.02 – 0.06 medium, and > 0.06 large. p ≤ 0.05 is represented by *.*

Partial eta squared (p-values)	**Group**	**Covariates**		
	OSA vs. control	**Sex**	**Age**	**BMI**
Model 1: Rest BR	0.02 (*p*=0.1)	0.03 (*p*=0.23)	0.00 (*p*=0.7)	*0.03 (*p*=0.04)
Model 2: Rest BRV	*0.04 (*p*=0.02)	0.015 (*p*=0.3)	0.01 (*p*=0.4)	0.02 (*p*=0.3)
Model 3: Change in BRV with BH	*0.1 (*p* =0.0005)	0.005 (*p*=0.7)	0.005 (*p*=0.6)	*0.1 (*p*=0.0003)

Table 3. Correlation of BMI with respiration variables.

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 <0.05. Significant Pearson's R correlation coefficients are italicized.

BMI correlation with->	Rest BR	Rest BRV	Change in BRV with BH
OSA (n=31)	R= *0.36 (p=0.04)*	R= *-0.37 (p=0.04)*	R= *-0.51 (p=0.003)*
Control (n=31)	R= 0.10 ((*p*=0.51)	R= -0.09 (*p*=0.63)	R= -0.18 (*p*=0.33)

Figure 1

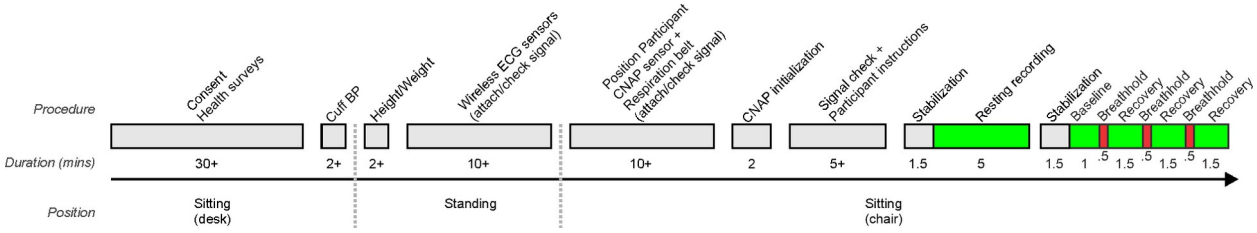

Procedure
Duration (mins)
Position
Consent
Health surveys
Cuff BP
Height/Weight
Wireless ECG sensors
(attach/check signal)
Position Participant
CNAP sensor +
Respiration belt
(attach/check signal)
CNAP initialization
Signal check +
Participant instructions
Stabilization
Resting recording
Stabilization
Baseline
Breathhold
Recovery
Breathhold
Recovery
Breathhold
Recovery
30+
2+
2+
10+
10+
2
5+
1.5
5
1.5
1
.5
1.5
.5
1.5
.5
1.5
Sitting
(desk)
Standing
Sitting
(chair)

Figure 2.

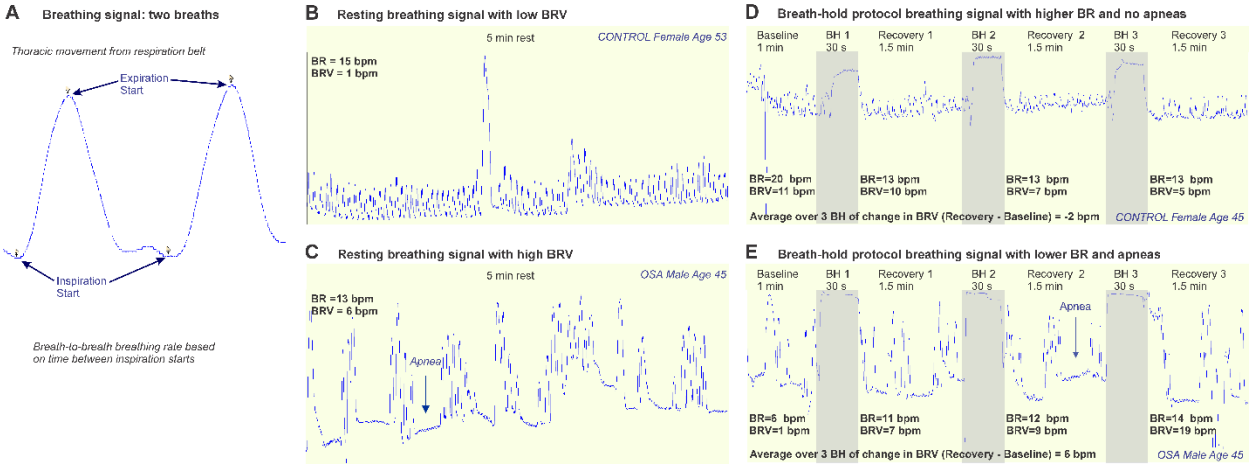
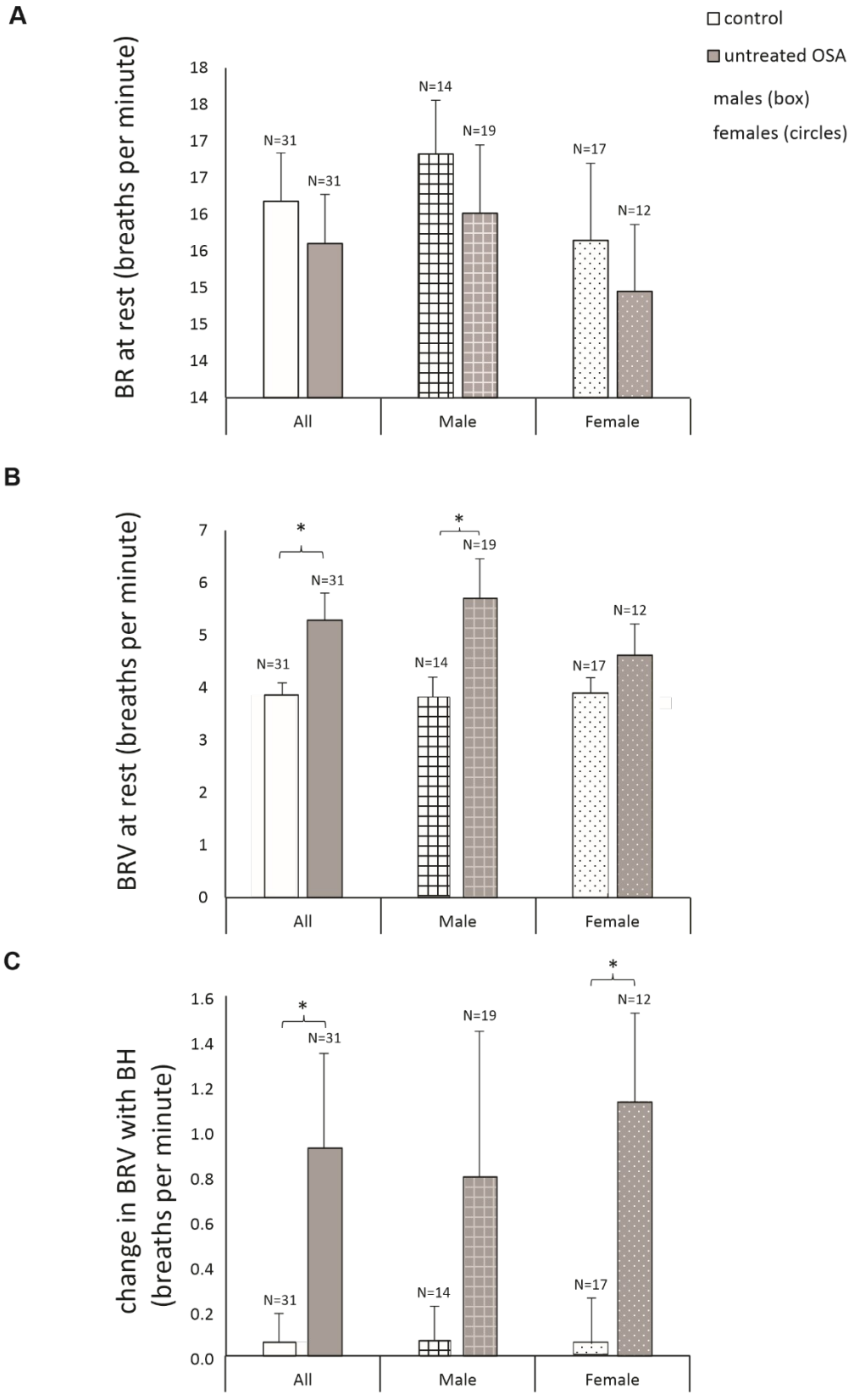

A
Breathing signal: two breaths
Thoracic movement from respiration belt
Expiration Start
Inspiration Start
Breath-to-breath breathing rate based on time between inspiration starts
B
Resting breathing signal with low BRV
5 min rest
CONTROL Female Age 53
BR = 15 bpm
BRV = 1 bpm
C
Resting breathing signal with high BRV
5 min rest
OSA Male Age 45
BR =13 bpm
BRV = 6 bpm
Apnea
D
Breath-hold protocol breathing signal with higher BR and no apneas
Baseline 1 min
BH 1 30 s
Recovery 1 1.5 min
BH 2 30 s
Recovery 2 1.5 min
BH 3 30 s
Recovery 3 1.5 min
BR=20 bpm
BRV=11 bpm
BR=13 bpm
BRV=10 bpm
BR=13 bpm
BRV=7 bpm
BR=13 bpm
BRV=5 bpm
Average over 3 BH of change in BRV (Recovery - Baseline) = -2 bpm
CONTROL Female Age 45
E
Breath-hold protocol breathing signal with lower BR and apneas
Baseline 1 min
BH 1 30 s
Recovery 1 1.5 min
BH 2 30 s
Recovery 2 1.5 min
BH 3 30 s
Recovery 3 1.5 min
Apnea
BR=5 bpm
BRV=1 bpm
BR=11 bpm
BRV=7 bpm
BR=12 bpm
BRV=9 bpm
BR=14 bpm
BRV=19 bpm
Average over 3 BH of change in BRV (Recovery - Baseline) = 6 bpm
OSA Male Age 45

Figure 3.


A
control
untreated OSA
males (box)
females (circles)
BR at rest (breaths per minute)
18
18
17
17
16
16
15
15
14
14
N=31
N=31
N=14
N=19
N=17
N=12
All
Male
Female
B
BRV at rest (breaths per minute)
7
6
5
4
3
2
1
0
*
*
N=31
N=31
N=14
N=19
N=17
N=12
All
Male
Female
C
change in BRV with BH (breaths per minute)
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
*
*
N=31
N=31
N=14
N=19
N=17
N=12
All
Male
Female