# Baroreflex sensitivity during rest and pressor challenges in obstructive sleep apnea patients with and without CPAP☆

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## ARTICLE INFO

## ABSTRACT

*Introduction:* Obstructive sleep apnea (OSA) increases sympathetic vasoconstrictor drive and reduces baroreflex sensitivity (BRS), the degree to which blood pressure changes modify cardiac output. Whether nighttime continuous positive airway pressure (CPAP) corrects BRS in the awake state in OSA remains unclear. We assessed spontaneous BRS using non-invasive continuous BP and ECG recordings at rest and during handgrip and Valsalva challenges, maneuvers that increase vasoconstrictor drive with progressively higher BP, in untreated OSA (unOSA), CPAP-treated OSA (cpOSA) and healthy (CON) participants.
*Methods:* In a cross-sectional study of 104 participants, 34 unOSA (age mean±std, 50.6±14.1years; Respiratory Event Index [REI] 21.0±15.3 events/hour; 22male), 31 cpOSA (49.6±14.5years; REI 23.0±14.2 events/hour; 22male; self-report 4+hours/night,5+days/week,6months), and 39 CON (42.2±15.0years; 17male), we calculated BRS at rest and during handgrip and Valsalva. Additionally, we correlated BP variability (BPV) with BRS during these protocols.
*Results:* BRS in unOSA, cpOSA and CON was, respectively (mean±sdv in ms/mmHg), at rest: 14.8±11.8, 15.8±17.0, 16.1±11.3; during handgrip 13.3±7.6, 12.7±8.4, 16.4±8.7; and during Valsalva 12.7±8.0, 11.5±6.6, 15.1±8.9. BRS was lower in cpOSA than CON for handgrip ($p=0.04$) and Valsalva ($p=0.03$). BRS was negatively correlated with BPV in unOSA during Valsalva and handgrip for cpOSA, both R=−0.4 ($p=0.02$). BRS was negatively correlated with OSA severity (levels: none, mild, moderate, severe) at R=−0.2 ($p=0.04$,n=104).
*Conclusions:* As expected, BRS was lower and BPV higher in OSA during the pressor challenges, and disease severity negatively correlated with BRS. In this cross-sectional study, both CPAP-treated (self-reported) and untreated OSA showed reduced BRS, leaving open whether within-person CPAP improves BRS.

## 1. Introduction

Autonomic regulation is altered in obstructive sleep apnea (OSA) during both sleep [1] and wakefulness [2,3]. For example, sympathetic outflow is high as reflected in greater muscle sympathetic nerve activity (MSNA) [1], which, over time, often leads to hypertension [4]. The high blood pressure accompanying OSA is commonly treatment-resistant to both anti-hypertensive medications and continuous positive airway pressure (CPAP) [5]. Regular use of CPAP does normalize MSNA, suggesting that other impairments, perhaps vascular remodeling or long-term neural injury to cardiac regulatory areas of the brain, contribute to the hypertension. Insight into these impairments may be gained from understanding autonomic mechanisms in treated and untreated OSA, in

**Abbreviations**

| | |
|---|---|
| AASM | American Academy of Sleep Medicine |
| ANS | autonomic nervous system |
| BMI | body mass index |
| BP | blood pressure |
| BPV | mean arterial blood pressure variability |
| BRS | Baroreflex sensitivity |
| CON | control |
| CPAP | continuous positive airway pressure |
| cpOSA | CPAP-treated OSA |
| CVD | cardiovascular disorders |
| HR | heart rate |
| HRV | heart rate variability |
| HSAT | home sleep apnea testing |
| MBP | mean arterial blood pressure |
| MSNA | muscle sympathetic nerve activity |
| OSA | obstructive sleep apnea |
| REI | respiratory event index |
| RR–I (t) | RR–interval or heart period |
| SBP | systolic blood pressure |
| unOSA | untreated OSA |

particular, the baroreflex. The baroreflex operates to maintain blood pressure (BP) relatively constant via changes in cardiac output and total peripheral resistance, and can be assessed by measurement of baroreflex sensitivity (BRS) [1,6,7]. Extensive structural injury occurs in the brain in OSA [8–10], including the brainstem where the essential circuitry responsible for the baroreflex is located [11–14]. Moreover, in OSA there are significant changes in functional activity related to BP control in the brain, as revealed through MSNA-coupled fMRI [15]. However, there is some evidence that the structural and functional changes may be partially reversed following 6 months of CPAP [16,17]. Therefore, we tested the hypothesis that baroreflex function is unimpaired in OSA patients using CPAP.

The baroreflex acts to maintain blood pressure within a narrow homeostatic range, although the set-point changes depending on physiological demands, such as during exercise [18]. It operates as a negative-feedback system in which stretch-sensitive baroreceptors located in the carotid sinus and aortic arch relay sensory information via the glossopharyngeal and vagus nerves to the nucleus tractus solitarius (NTS) in the medulla. From there, excitatory synapses are made with the nucleus ambiguus (NA) and the dorsal motor nucleus of the vagus (DMNV), which send excitatory projections to the parasympathetic ganglia of the heart. Those neurons within the ganglia can reduce the rate and force of cardiac contraction. Excitatory neurons in NTS also send excitatory projections to the caudal ventrolateral medulla (CVLM), which makes inhibitory synapses with the bilateral rostral ventrolateral medulla (RVLM), the final output nuclei for generating bursts of MSNA [19,20]. The baroreflex is often impaired in cardiovascular diseases [21], including OSA [22], and in neurological disorders [12]. A failure at any level of the reflex arc–baroreflex afferent/central/efferent pathway could affect baroreflex function, resulting in exaggerated or depressed BRS [23].

Depressed BRS appears in untreated OSA patients [24], but there is evidence CPAP treatment improves baroreflex control during sleep in OSA [25]. Whether this improvement extends to the awake state is unclear; during wakefulness, OSA patients show augmented sympathetic activity as reflected by increased MSNA [26,27]. Additionally, during wakefulness, OSA patients show a decreased

sympathetic component of the BRS as measured by how effectively the baroreflex buffers beat-to-beat changes in blood pressure through modulation of MSNA. OSA also shows decreased BRS as measured by the sensitivity of baroreflex control of the heart assessed using the relationship between R-R interval and systolic blood pressure (sometimes called "cardiac" BRS) [28]. However, other studies have found that although OSA patients show depressed sympathetic components of the BRS, they did not differ from healthy people in cardiac BRS [29]. The focus here is on cardiac BRS, which we refer to just as BRS. As an aside, depressed BRS is often associated with higher severity of OSA [30], but mild-to-moderate OSA does not always show depressed BRS [6]. Regardless, when impaired BRS is present, it could presumably contribute to the development of cardiovascular disease independently of what happens during sleep. Long-term CPAP treatment has been thought to improve baroreflex dysfunction in OSA partly by resolving nocturnal intermittent hypoxia [31]. MSNA during waking is reduced to healthy levels with continual CPAP treatment for 6 months [32], an improvement that may arise from restoration of brainstem autonomic structures and function [16,33]; however, it is unclear if treatment resolves baroreflex dysfunction in OSA during wakefulness.

The baroreflex is recruited with any pressor challenge, such as handgrip or Valsalva [34–36], including in OSA [37]. BRS has been evaluated during rest and in response to exercise training using continuous BP and ECG recordings in OSA participants [38]. During a standard handgrip challenge, after 15–30 s of isometric gripping, BP and heart rate (HR) increase [35,36]. During a Valsalva maneuver, HR and BP increase after 10–20 s of forced expiration and, upon release, change with a distinct rapid fluctuation (Phase III) and longer recovery (Phases IV); these responses differ in OSA compared with healthy people [39,40]. These well-characterized BP changes elicited with standard challenges provide an opportunity to test the BRS.

Low BRS normally leads to high BP variability (BPV), since the weaker regulation results in exaggerated BP fluctuations [41,42]. This relationship is consistent with observations in OSA of high BPV [2,43] and low BRS [1,28]. Thus, in OSA any reduced BRS during wakefulness should be associated with an increase in BPV.

One further consideration is sex differences. Previously, we showed a higher BPV in females with OSA [2], which could result from a more depressed BRS in women as opposed to men with OSA [44]. Sex differences were observed in the insular cortex in response to handgrip [45]; however, no OSA-specific difference was observed in the functional response of the insula to handgrip irrespective of sex [46]. Given that the early increase in HR during handgrip is believed to be due to withdrawal of cardiac vagal drive, this parasympathetic withdrawal contribution to HRV in response to a standardized handgrip challenge has been proposed to remain the same in OSA as in healthy people irrespective of sex [46]. However, the insula responses to the Valsalva showed OSA-specific effects in only in females, who showed greater right anterior dominance [39]. These variable findings reinforce the importance of considering sex differences when assessing autonomic function in OSA.

The objective here was to quantify BRS during wakefulness in untreated OSA (unOSA), CPAP-treated OSA (cpOSA) and healthy controls (CON) during rest, handgrip and Valsalva, while accounting for sex. Additionally, we aimed to quantify the association between BRS and BRV. As a first step, we performed a study with a cross-sectional design. We hypothesized BRS would show group differences between each combination of unOSA, cpOSA, and CON. We also hypothesized that BPV would be inversely related to BRS.

**Table 1**

Participant details.

Participant characteristics by group and sex. Measures are presented as mean±stdev [range]. BMI: body mass index; CON: control; cpOSA: CPAP-treated OSA; unOSA: untreated OSA; REI: respiratory event index.

| | unOSA | | | cpOSA | | | CON | | |
|---|---|---|---|---|---|---|---|---|---|
| | All (N= 34) | Males (N= 22) | Females (N= 12) | All (N= 31) | Males (N= 22) | Females (N= 9) | All (N= 39) | Males (N=17) | Females (N= 22) |
| Age (years)† | 50.6±14.2 [25−77] | 47.4±13.7 [25−77] | 56.5±13.6 [34−77] | 49.6±14.5 [27−73] | 46.0±14.2 [27−71] | 57.9±12.2 [31−73] | 42.1±15.0 [21−67] | 42.1±16.5 [23−67] | 42.2±14.4 [21−66] |
| BMI (kg/m$^2$) | 32.8±8.0 [21.9−54.3] | 32.8±7.3 [22.2−47.0] | 31.7±7.40 [21.9−54.3] | 29.4±5.5 [19.6−42] | 28.4±4.4 [19.6−38.3] | 29.4±5.5 [22.6−42] | 26.0±4.3 [19.6−37.6] | 27.2±3.6 [21.8−33.2] | 25.2±4.7[19.6−37.6] |
| **Sleep parameters** | | | | | | | | | |
| REI (events/hour) | 21.1±15.3 [6.0−67.4] | 19.1±10.7 [6.0−42.0] | 24.7±21.3 [6.9−67.4] | 22.5±13.9 [5.0−58] | 21.4±13.9 [5.0−58.0] | 25.5±14.3 [6.0−45.9] | | | |
| Mean oxygen saturation (%) | 94.8±1.5 [91−96.5] | 94.2±2.3 [90.0−99.9] | 94.8±1.5 [92.0−96.5] | 94.0±2.2 [91.0−96.5] | 94.8±1.6 [91.0−96.4] | 93.8±2.2 [92.0−96.5] | | | |
| Minimum oxygen saturation (%) | 83.6±5.8 [68.8−92.0] | 83.6±5.5 [68.8−92.0] | 82.4±7.1 [67.0−91.4] | 82.7±9.0 [68.8−92.0] | 82.4±7.1 [68.8−92.0] | 83.4±13.4 [70.9−92.0] | | | |

†$p<0.01$ differences in age between CON and both OSA groups (unOSA and cpOSA). No significant difference was present between unOSA and cpOSA.
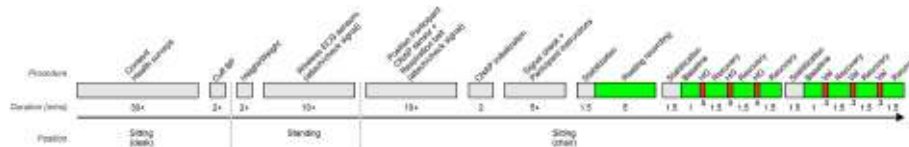


**Fig. 1.** Protocol timeline.

Protocol timeline showing procedure (top), duration in minutes (middle) and participant position (bottom). Colored areas show data used for analysis, with green indicating rest or baseline and recovery, and red indicating tasks. BP = blood pressure; CNAP = continuous non-invasive arterial pressure; ECG = electrocardiogram; HG= Handgrip; Val= Valsalva. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

## 2. Methods

*Design:* We performed a cross-sectional study of three groups based on a convenience sample.

*Recruitment and screening:* Recruitment fliers were posted on the UCLA campus and in the UCLA Sleep Disorders Center, and on online sites advertising UCLA research studies. Fliers for untreated OSA participants targeted people with confirmed or suspected OSA, fliers for treated OSA targeted people using CPAP, and fliers for control participants targeted healthy people. Participants in the OSA groups had their sleep disorder diagnosed by the UCLA Sleep Disorders Center via an at-home test.

After initiating contact, potential participants underwent a phone screening followed by a more comprehensive online survey to assess eligibility. Phone screening included questions about diagnosed sleep disorders, sleep complaints, mental health disorders, or snoring. Participants who passed the phone screening completed an online questionnaire that included questions about medical history, sleep disorders, sleep complaints, menopausal status, and daytime sleepiness. Participants reporting daytime sleepiness or other sleep complaints were given a two−night home sleep apnea testing (HSAT) through the UCLA Sleep Disorders Center to screen for OSA and other sleep disorders. Exclusion criteria for all participants included sleep disorders other than OSA, major illness or head injury, stroke, major cardiovascular disease, current tobacco use, recent (< 3 months) use of psychotropic 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). Hypertension was reported in ten people (four cpOSA, four unOSA and two CON).
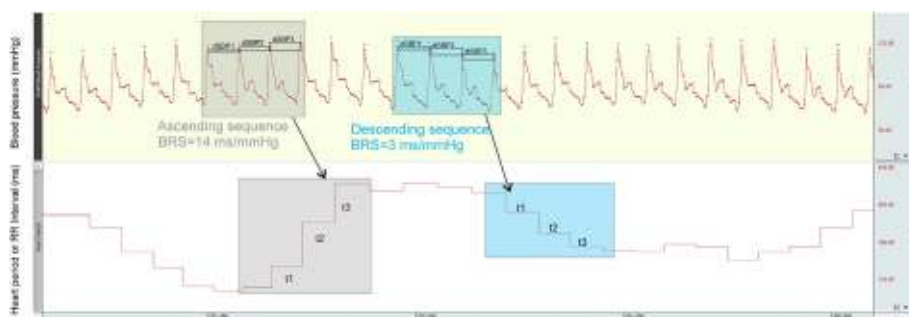


**Fig. 2.** Sample traces illustrating baroreflex sensitivity (BRS) calculation.

Illustration of the BRS sequence analysis method in Acqknowledge 5.0. Ascending and descending sequences are defined as at least three cycles showing changes in blood pressure of at least 0.5 mmHg and changes in RR interval of at least 1 ms. For each systolic blood pressure (SBP)-to-SBP change (dSBP), the corresponding change in RR interval (t) is extracted, and the BRS is calculated as the absolute value of the regression coefficient of the change in t over dSBP over the sequence.
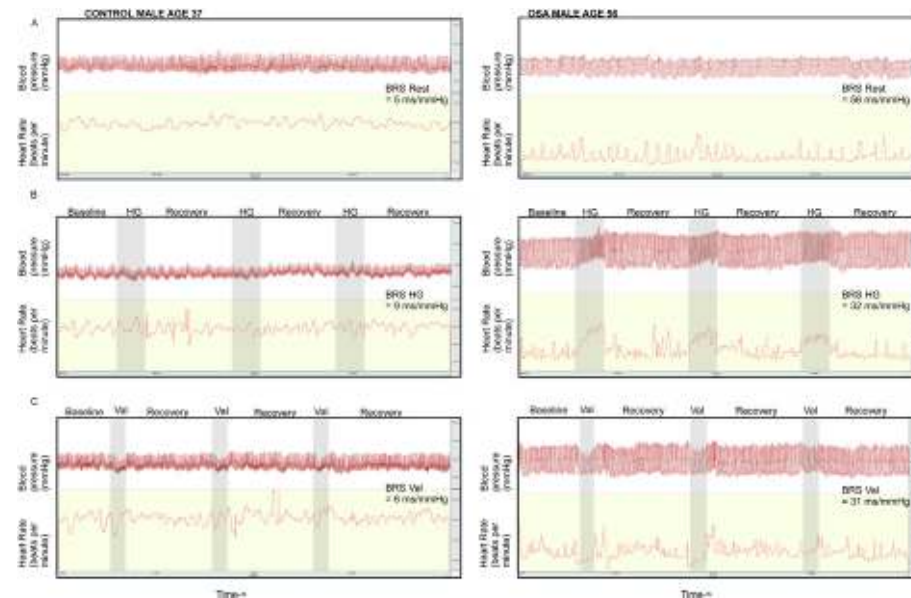
**Fig. 3.** Sample traces in control and OSA participants illustrating baroreflex sensitivity (BRS) in different task periods.
Examples illustrating blood pressure (BP) and heart rate (HR) patterns associated with a range of BRS values during rest (top row), handgrip (HG; middle row) and Valsalva (Val; bottom row), in control (left column) and untreated OSA (right column) participants. The x- and y-axes were similarly scaled in all graphs. Shaded areas show when a task (handgrip or Valsalva) was performed.

*Sample:* We enrolled 34 unOSA, 31 cpOSA and 39 CON participants (Table 1). There were significant age differences between groups, with CON younger than OSA. There were 15 unOSA and 11 cpOSA participants diagnosed with mild OSA, 11 unOSA and 8 cpOSA participants diagnosed with moderate OSA, and, 8 unOSA and 12 cpOSA participants diagnosed with severe OSA. Some of these participants were studied previously [2]. CPAP usage was self-reported and adherence of 4+ hours/night at least five days/week for at-least 6 months was set as the inclusion criteria for the cpOSA group.

*Ethics:* All procedures were approved by the UCLA Institutional Review Board. All participants provided written informed consent.

*Sleep studies:* Participants without a recent diagnosis (<6 months) or with suspected OSA were referred for an HSAT with an ARES™ device (https://sleepmedinc.com/sleep-solutions/ares-home-testing/) [47]. ARES™ has the electrodes frontopolar (FP)1 and FP2 for deriving EEG, electro-oculogram (EOG) and electromyogram (EMG), but it does not qualify for the American Academy of Sleep Medicine (AASM) definition of HSAT sleep vs wake states; the device allows for calculating the respiratory event index (REI) as opposed to the apnea–hypopnea index (AHI). The ARES device captures airflow using a nasal cannula and pressure transducer. Apnea was defined as a cessation (> 90% reduction) in flow for $\geq$ 10 seconds, hypopnea $\geq$ 50% reduction in flow for $\geq$ 10 seconds; the criterion for REI apneas and hypopneas was 4% desaturation [48]. The scoring assigned to participants was based on the average over the single night with the longest valid recording time. The unOSA participants were not using CPAP or any other treatment for the sleep disorder, although since the sleep studies were not performed at the same time as data collection (mean $\pm$ SD time difference between physiology and sleep study = 25.1 $\pm$ 26.6 days), the group included people who had been offered but did not use CPAP.

Thirteen people in the control group had HSAT sleep studies and one person was diagnosed with OSA, and categorized as unOSA. In the remaining 12 control participants, the REI mean $\pm$ SD was 0.5$\pm$0.8 events/hr, minimum oxygen saturation was 89$\pm$6% and
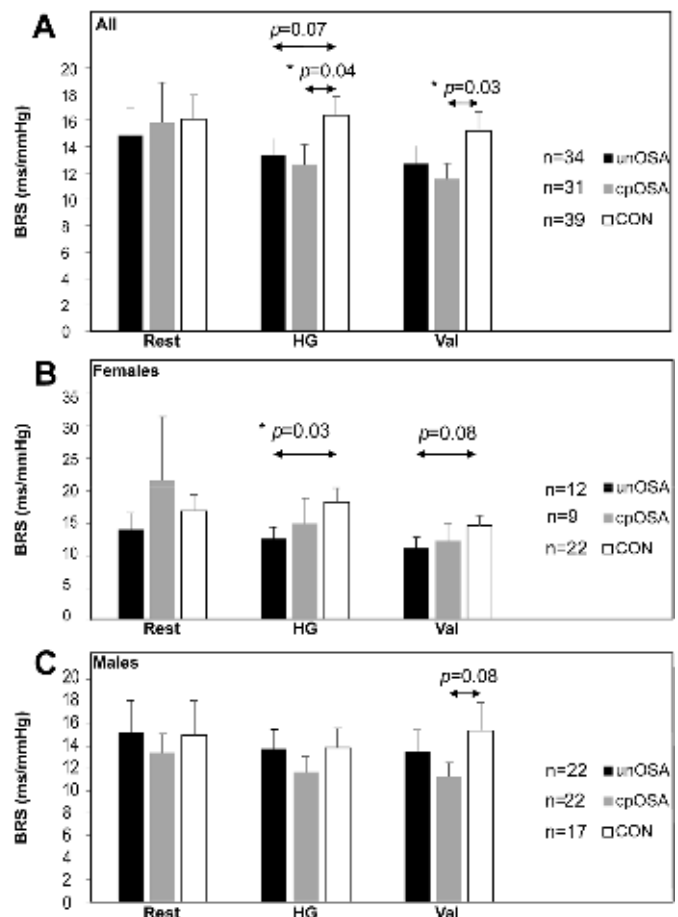


**Fig. 4.** BRS changes during tasks.
BRS mean $\pm$ SEM values during rest, handgrip (HG) and Valsalva (Val) are shown in untreated OSA (unOSA), CPAP treated OSA (cpOSA), and control (CON) in combined (A), female (B), and male (C) groups. *p*–values from independent two sample t-tests are shown (*$\leq$0.05).

**Table 2**

Physiological measures.

The main outcome variable of BRS (ms/mmHg) and secondary outcome variable BPV (mmHg) during rest, handgrip (HG) and Valsalva (Val) for unOSA, cpOSA and CON are presented as mean±stdev [range]. Significance values for two-group comparisons using independent two-sample t tests are shown, with $p < 0.05$, $p < 0.01$ and $p < 0.001$ indicated by *, ** and ***, respectively. BPV: blood pressure variability; BRS: baroreflex sensitivity; CON: control; cpOSA: CPAP-treated OSA; unOSA: untreated OSA.

| All | unOSA (N=34: 15 mild, 11 moderate, 8 severe) | cpOSA (N=31: 11 mild, 8 moderate, 12 severe) | CON (N=39) | † | ‡ | †† |
|---|---|---|---|---|---|---|
| BRS at rest (ms/mmHg) | 14.8±11.8 [3.6−56.5] Mild: 12.8±8.7 Moderate: 16.9±15.5 Severe: 16.0±11.8 | 15.8±17.0 [1.9−98.3] Mild: 21.5±27.2 Moderate: 13.3±8.0 Severe: 12.2±4.1 | 16.1±11.3 [1.7−46.5] | 0.34 | 0.47 | 0.41 |
| BRS at HG (ms/mmHg) | 13.3±7.6 [3.5−31.7] Mild: 13.6±7.1 Moderate: 13.6±7.5 Severe: 12.5±9.3 | 12.7±8.4 [1.9−39.0] Mild: 14.6±10.0 Moderate: 9.5±5.1 Severe: 12.9±7.9 | 16.4±8.7 [1.6−43.6] | 0.07 | *0.04 | 0.35 |
| BRS at Val (ms/mmHg) | 12.7±8.0 [2.4−31.3] Mild: 13.4±7.6 Moderate: 13.5±9.2 Severe: 10.3±7.9 | 11.5±6.6 [1.9−29.0] Mild: 12.3±7.1 Moderate: 12.4±6.6 Severe: 10.3±7.3 | 15.1±8.9 [2.6−41.8] | 0.11 | *0.03 | 0.27 |
| BPV at rest (mmHg) | 2.8±0.8 [1.2−5.1] Mild: 2.9±0.9 Moderate: 2.8±0.6 Severe: 2.6±1.1 | 2.5±0.8 [0.8−4.4] Mild: 2.5±0.8 Moderate: 2.7±0.5 Severe: 2.3±1.1 | 2.8±0.8 [0.9−5.7] | 0.36 | 0.14 | *0.05 |
| BPV at HG (mmHg) | 4.4±1.9 [2.5−9.3] Mild: 4.2±1.9 Moderate: 4.9±1.9 Severe: 3.8±1.7 | 4.3±2.2 [1.9−9.5] Mild: 4.9±2.3 Moderate: 5.0±2.6 Severe: 3.3±1.7 | 3.8±2.4 [1.7−14.2] | 0.12 | 0.17 | 0.46 |
| BPV at Val (mmHg) | 7.0±2.4 [2.9−13.8] Mild: 7.2±3.2 Moderate: 6.8±1.5 Severe: 6.8±1.7 | 5.7±1.8 [3.3−10.8] Mild: 5.3±1.7 Moderate: 6.5±2.1 Severe: 5.4±1.6 | 5.3±1.4 [3.3−9.1] | ***0.0006 | 0.2 | **0.008 |
| **Males** | unOSA (N=22) | cpOSA (N=22) | CON (N=17) | † | ‡ | †† |
| BRS at rest (ms/mmHg) | 15.3±13.7 [3.6−56.5] | 13.4±8.0 [1.9−32.5] | 15.0±10.7 [1.6−43.5] | 0.47 | 0.31 | 0.29 |
| BRS at HG (ms/mmHg) | 13.8±8.3 [2.1−31.7] | 11.7±6.7 [1.8−27.8] | 13.8±6.1 [2.6−21.5] | 0.48 | 0.15 | 0.18 |
| BRS at Val (ms/mmHg) | 13.1±7.6 [2.1−31.7] | 13.7±9.0 [1.8−39.0] | 18.3±11.9 [3.1−62.9] | 0.28 | 0.08 | 0.16 |
| BPV at rest (mmHg) | 3.1±0.8 [1.8−5.1] | 2.6±0.8 [0.8−4.4] | 2.7±1.1 [1.0−4.7] | 0.22 | 0.36 | 0.08 |
| BPV at HG (mmHg) | 4.6±2.0 [2.6−9.3] | 4.5±2.2 [2.4−9.5] | 3.7±1.4 [1.7−7.7] | 0.06 | 0.10 | 0.43 |
| BPV at Val (mmHg) | 7.1±1.9 [3.4−11.5] | 5.9±1.9 [3.3−10.8] | 5.5±1.4 [3.3−8.7] | **0.003 | 0.25 | *0.03 |
| **Females** | unOSA (N=12) | cpOSA (N=9) | CON (N=22) | † | ‡ | †† |
| BRS at rest (ms/mmHg) | 14.1±8.8 [4.1−32.6] | 21.5±29.6 [3.3−98.3] | 16.9±11.8 [2.8−46.5] | 0.22 | 0.33 | 0.24 |
| BRS at HG (ms/mmHg) | 12.6±6.4 [5.2−25.7] | 14.9±11.8 [4.6−38.9] | 18.2±10.0 [4.9−43.6] | *0.03 | 0.23 | 0.30 |
| BRS at Val (ms/mmHg) | 11.1±6.1 [4.6−25.1] | 12.3±12.2 [3.8−26.5] | 14.6±7.7 [3.9−33.8] | 0.08 | 0.24 | 0.36 |
| BPV at rest (mmHg) | 2.5±0.7 [1.2−3.6] | 2.1±0.8 [1.3−3.7] | 2.7±1.2 [0.9−5.7] | 0.24 | *0.05 | 0.14 |
| BPV at HG (mmHg) | 3.9±1.6 [2.5−7.0] | 3.9±2.2 [1.9−8.4] | 3.9±2.5 [1.9−14.2] | 0.49 | 0.48 | 0.47 |
| BPV at Val (mmHg) | 6.7±3.1 [2.8−13.8] | 5.1±1.4 [3.9−8.1] | 5.3±1.5 [3.4−9.2] | 0.07 | 0.37 | 0.06 |

† *p*-value unOSA vs. CON, ‡ *p*-value cpOSA vs. CON, †† *p*-value unOSA vs. CPAP.

**Table 3**

**Correlations between BRS and BPV.**

The Person R correlation values for BRS (ms/mmHg) and BPV (mmHg) for unOSA, cpOSA and CON are presented during rest, handgrip (HG) and Valsalva (Val). * indicates $p < 0.05$ as per Fisher Z-transformation. BPV: blood pressure variability; BRS: baroreflex sensitivity; CON: control; cpOSA: CPAP-treated OSA; unOSA: untreated OSA.

| Correlation of BRS and BPV | All | | | Male | | | Female | | |
|---|---|---|---|---|---|---|---|---|---|
| Tasks | R, unOSA N = 34 | R, cpOSA N = 31 | R, CON N = 39 | R, unOSA N = 22 | R, cpOSA N = 22 | R, CON N = 17 | R, unOSA N = 12 | R, cpOSA N = 9 | R, CON N = 22 |
| Rest | −0.03 | −0.21 | −0.04 | 0.14 | −0.06 | 0.21 | −0.67* | −0.29 | −0.20 |
| HG | −0.14 | −0.41* | −0.23 | −0.08 | −0.41 | 0.37 | −0.38 | −0.43 | −0.41 |
| Val | −0.37* | −0.24 | −0.26 | −0.36 | −0.38 | −0.21 | −0.53 | 0.09 | −0.30 |

average oxygen saturation was 96±2%.

*Protocol:* Participants were asked to avoid caffeine or other stimulants 24 h 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 a.m. earliest) to early evening (6:30 p.m. latest start). We measured participants' height and weight for BMI calculation, and recorded resting BP (Omron 3 series BP monitor, Kyoto, Japan). We obtained ECG and beat-to-beat continuous non-invasive arterial pressure (CNAP Monitor 500, CNSystems, Berlin, Germany). Automated finger cuffs and brachial BP cuffs were placed on the participant's left middle and index fingers and their left upper arm at the brachial artery, respectively. Three
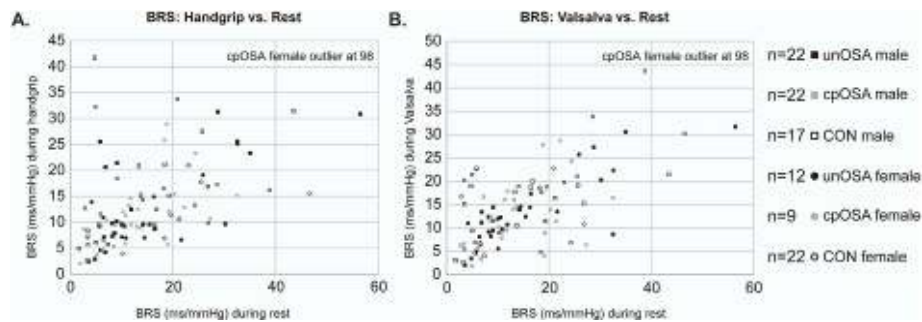
**Fig. 5.** BRS correlations between rest and task.
Scatterplots of BRS (ms/mmHg) of (A) Valsalva vs rest, and (B) handgrip vs rest in untreated OSA (unOSA), CPAP treated OSA (cpOSA), and control (CON).

ECG electrodes were placed on the participant's torso according to standard placements. Continuous data were collected with BIO-PAC's MP150 system (BIOPAC Systems Inc, Goleta, CA, USA). The CNAP monitor is based on pressure at the finger, and is calibrated with an automatically-obtained brachial cuff measure ("CNAP initialization" in Fig. 1) [2]. At initialization, the CNAP signal is matched to the brachial cuff values. We used the CNAP v3.5 protocol with adult default settings (https://www.biopac.com/wp&ndash;content/uploads/nibp100d_cnap_monitor.pdf) [49]. The filter setting on the CNAP acquisition was 1 kHz low pass. All data were sampled at 1 kHz.

Fig. 1 demonstrates the data acquisition timeline. The rest protocol consisted of 5 min' seated resting physiologic data, following a 90 s stabilization period. The handgrip protocol involved three challenge periods at 80% of maximum grip strength using an electric handgrip dynamometer. After 60 s of baseline stabilization, there were 30 s of handgrip followed by 90 s of recovery, repeated twice for a total of three times (60 s baseline, 90 s recovery, 80% maximum strength), resulting in a 7 min protocol. Maximum grip strength was calculated earlier in the session based on the average of three attempts to grip as hard as possible. Participants viewed a real-time display of their grip strength relative to the target, and were instructed to maintain grip levels just above the target. The Valsalva protocol involved three challenge periods with target of 30 mmHg expiratory pressure. After 60 s of baseline stabilization, there were 16 s of Valsalva followed by 90 s of recovery, repeated for a total of three times. A visual display was used to guide participants to maintain the target pressure.

*Analysis—BRS calculation:* An index of baroreflex sensitivity (BRS) is the millisecond increase in inter-beat RR-interval per mmHg change in BP [34]. The RR-interval was calculated from R-waves of the ECG using "Acqknowledge" 5.0 software with manual verification of all peaks (BIOPAC Systems Inc, Goleta, CA, USA). Spontaneous baroreflex sensitivity (BRS) in the time domain can be measured from sequences of beats in which the absolute changes between consecutive ascending or descending systolic pressure values are greater than a given threshold; the corresponding ECG waves allow calculation of the corresponding HR changes in th sequence [21,50]. Fig. 2 demonstrates the BRS calculation for an ascending and descending sequence. The change in R-R intervals occurred about 1 ms after at least 0.5 mmHg change in systolic BP (* in Fig. 2) in at least three consecutive cycles, as per the BRS sequence method implemented in Acqknowledge 5.0. For each SBP-to-SBP change (dSBP), the corresponding change in RR interval (t) is extracted, and the BRS is calculated as the regression coefficient of change in t over change in SBP in an ascending or descending sequence of at least three consecutive data points, similar to another OSA study [38]. Here, sequences of greater than three beats of either progressive increases or decreases in systolic

BP and RR that were well-correlated ($R \geq 0.7$) were identified. The mean slope of the regression line between these parallel sequences was calculated and used to represent the BRS, in units of ms/mmHg [18,51]. In one study, the optimal shortest recording time for BRS estimation in an orthostatic position was calculated to be $3.74 \pm 0.07$ min, with accuracy decreasing with shorter recording times [52]. For longer durations, the R-value threshold for well-correlated sequences was greater than 0.7 for a duration of 5 min [53,54].

*Analysis—measures:* BRS was determined for rest, handgrip and Valsalva protocols. The regressions for ascending and descending sequences were averaged to obtain a measure of BRS during each of the the 5 min rest and two 7 min challenge periods. Fig. 3 demonstrates the average of ascending and descending sequence BRS for the periods of rest, handgrip, and Valsalva in healthy and OSA participants.

BPV was calculated from the continuous BP signal [2]. In brief, we calculated the standard deviation of beat-to-beat mean arterial BP over each of the three protocols (rest, handgrip and Valsalva), resulting in three BPV measures for each subject.

*Statistics:* We calculated descriptive statistics for BPV and BRS in the three groups (unOSA, cpOSA and CON) for the three tasks (rest, handgrip, Valsalva). Although we had three groups, our interest was in two-way comparisons, so we tested for differences in means between each pair of groups. We performed group comparisons with independent two-samples t-tests, and BPV was correlated with BRS using Pearson R correlation. We used a statistical threshold of $p = 0.05$ significance. Although the study was not powered to assess within-sex effects, we presented sex-specific findings to allow consideration of female and male effect sizes.

## 3. Results

Resting BRS was not significantly different between groups (Fig. 4 and Table 2). Group BRS differences emerged during handgrip, with significantly lower values in both OSA groups compared with the control participants (unOSA mean±SEM ms/mmHg: 13.3±1.3; cpOSA: 12.7±1.5; CON: 16.4±1.4; Fig. 4 and Table 2). Similarly, OSA BRS was lower during Valsalva (unOSA mean±SEM ms/mmHg: 12.7±1.4; cpOSA: 11.5±1.2; CON: 15.1±1.4). BRS was negatively correlated with BPV in OSA during Valsalva for unOSA and during handgrip for cpOSA, both at $R = -0.4$ ($p < 0.05$; Table 3). BRS was negatively correlated with OSA severity (levels: none, mild, moderate, severe) at $R = -0.2$ ($p < 0.05$; Table 3).

Additional findings illustrate relationships of BRS with other variables. Scatterplots of pressor-induced BRS with BRS at rest illustrate associations across groups (Fig. 5). BPV (standard deviation of beat-to-beat BP) was similar across groups during rest and handgrip, but was significantly lower in CON during Valsalva
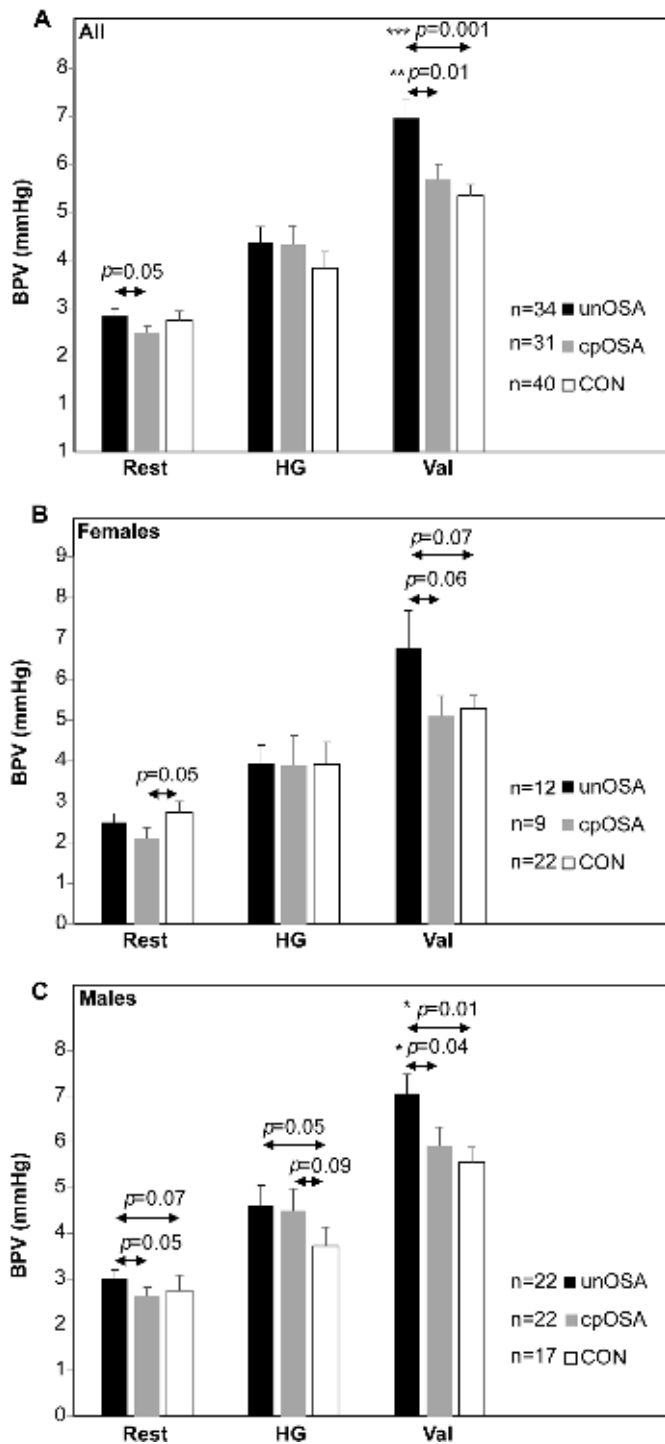
**Fig. 6.** BPV changes during tasks.
BPV mean ± SEM values during rest, handgrip (HG) and Valsalva (Val) are shown in untreated OSA (unOSA), CPAP treated OSA (cpOSA) and control (CON) in the combined sample (A), females (B) and males (C). *p*–values from independent two sample t-tests are shown (* <0.05, ** <0.01, *** <0.001).

(Table 2, Fig. 6). BRS was negatively correlated with BPV when assessed over all participants; however, in group-specific analyses, this relationship was only significant in unOSA during Valsalva (R = −0.4, p = 0.02) and in cpOSA during handgrip (also R = −0.4, p = 0.02) (Table 3, Fig. 7). BRS for handgrip and Valsalva correlated negatively with OSA severity when assessed in all participants (n = 104, levels: none, mild, moderate, severe) at R = −0.2, p = 0.04

(Table 2).

## 4. Discussion

We found that BRS is depressed in OSA relative to healthy participants irrespective of CPAP usage during the autonomic challenges of handgrip and Valsalva, but not at rest. The lack of depressed BRS during rest in OSA vs healthy is consistent with other studies [29]. Additionally, the range of disease severity in the present data may also contribute to only modest differences, since depressed BRS is strongly associated with severe OSA [55], but to a lesser degree with mild or moderate OSA [6]. In our sample, there were more-mild and moderate rather than severe cases in the untreated OSA group compared to the CPAP group, so this difference in severity may partially explain the more depressed BRS in CPAP vs untreated OSA. We did find BRS correlated negatively with OSA severity, consistent with previous studies [6,25,37]. These influences notwithstanding, in the present sample we did not find evidence to support the possibility that BRS is improved with CPAP.

Existing literature suggests that with increased OSA severity, higher sympathetic activity and decreased BRS are common even during wakefulness, and that CPAP treatment improves the baroreflex during sleep [1,6,25]. The findings here suggest that altered BRS during wakefulness may not be addressed by CPAP usage, a finding supported by some previous literature [56], although the cross-sectional nature of the present study limits this interpretation. CPAP in the present participants likely has some effect on autonomic function, since BPV in that group is lower than in untreated OSA during rest.

The reduced BRS in OSA was associated with patients taking longer to recover BP following handgrip and Valsalva as reflected in the negative correlation of BRS with BPV. However, the relationship between BRS and BPV was variable; BPV was higher untreated but not CPAP OSA or healthy controls. BP is typically higher in OSA [57], and bradycardia [58] and lowered HRV [59] are common. The altered resting HRV could be another reflection of the reduced BRS has shown during pressor challenges. These OSA effects may reflect a weakened response, rather than a missing or abnormal one, since we previously found that the insular functional organization during handgrip had similar pattern time-courses in OSA and CON groups, with only magnitude differences in the neural responses [46]. Overall, it appears that although OSA participants can respond to rapid changes in BP, the baroreflex function is less effective than in healthy people, leading to poor BP and HR control.

Depressed BRS may negatively affect cardiovascular health in OSA [60], which would be of particular concern if BRS does not resolve with CPAP, at least during wakefulness [61]. Although there are reports of restoration of BRS and autonomic functioning after CPAP [17], those reports should be considered in the context of resting levels versus particular autonomic challenges that modify BRS responsiveness. In normotensive OSA patients, sympathetic nervous system activity, based on norepinephrine excretion, is continuously increased and is not affected by short-term CPAP treatment [61]. Nevertheless, treatment presumably does help mitigate pathological physiology, as CPAP reduces sympathetic tone as measured by MSNA [15] and during sleep CPAP improves baroreflex function [24]. Over time, such benefits would presumably reduce the incidence or severity of cardiovascular disease.

The neural changes induced by OSA likely contribute at least in part to the processes underlying the baroreflex findings. OSA damages the insula, especially the right insula [9,10,39], and such damage is associated with depressed BRS and poor cardiac regulation generally [62–67]. The finding suggesting that CPAP may not correct that loss likely derives from that region-specific injury, and may imply long-term deficits; although glial cells may be replaced,
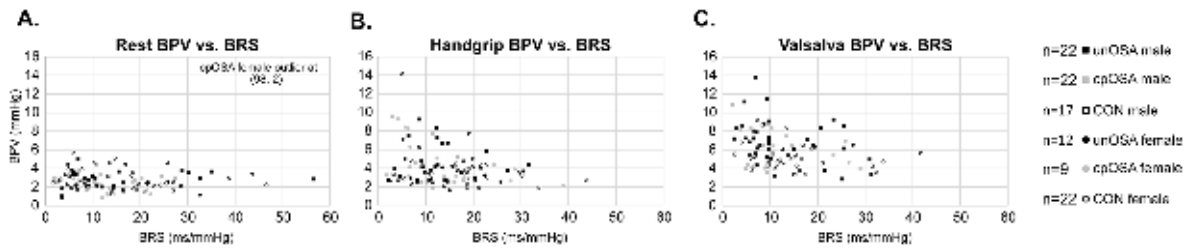
**Fig. 7.** BRS and BPV correlations.
Scatterplots of BPV (mmHg) vs BRS (ms/mmHg) in untreated OSA (unOSA), CPAP treated OSA (cpOSA), and control (CON) during (A) rest, (B) handgrip (HG) and (C) Valsalva (Val).

neurons in the insula are not [10]. Intermittent hypoxic injury in OSA appears in the deep cerebellar nuclei, cerebellar Purkinje cells, and the parabrachial pons; the same brain regions are known to control HRV [15,68—70]. One role of the deep cerebellar and parabrachial pontine nuclei is to integrate incoming afferent information from the lungs and other parts of the respiratory system with cardiovascular output processes [71], and with injury, that cardiovascular control is compromised in OSA [72]. BP control has several hierarchal levels; at rest, low level, reflexive mechanisms are prominent and may be less affected by OSA injury (because they operate in areas less affected by hypoxic injury). However, as in major non-rest conditions (challenges such as breathing stress and rapid BP changes), additional control processes are brought into action by cortical regions, including the insula, which are largely compromised in OSA. Determining the role of injured structures in contributing to BRS should be a goal of future studies.

*Limitations:* Any medication that alters BP could impact the overall findings of our study; we only excluded medicines known to have a major cardiovascular impact. Both OSA groups were older than the control groups, which presumably would have enhanced rather than obscured any disease-related differences. The CPAP adherence was self-reported, and it is possible the treated group included a range of hours/night and nights/week of usage. The similar ages of treated vs untreated groups mean that CPAP vs untreated comparisons were likely not unduly affected by age. As expected, the OSA group showed more signs of cardiovascular disease, with four participants in each of the OSA groups reporting hypertension vs two in the control group. The cross-sectional nature of the study limits any causal inferences. The mixture of mild, moderate and severe OSA patients likely diluted the findings that might be apparent in a severe group of patients, such as spontaneous BRS during rest which we would expect to be affected in that subgroup. Finally, the study was not powered to identify for sex differences, so the sex-specific findings should be considered trends that remain to be confirmed.

*Conclusions:* BRS was not reduced during rest in OSA, but was depressed during handgrip and Valsalva challenges. Higher BPV correlated with the decreased BRS during the autonomic challenges, suggesting impaired acute BP regulation in OSA. High OSA severity was a predictor of depressed BRS, consistent with existing literature [1,6]. The present findings do not provide evidence that CPAP addresses the depressed BRS in OSA in the awake state, despite previous indications that CPAP treatment alters the BRS during sleep, especially in severe OSA [24,25]. These findings raise the question of which mechanisms of cardiac regulation are resolved with CPAP, and which are based on other pathology such as brain injury that may need alternative treatments.

## Trail register

The manuscript does not report on a clinical trial.

## Grant support

## Declaration of competing interest

The authors declare that they have no conflict of interest.

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