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SCIENTIFIC INVESTIGATIONS

Beat-to-beat blood pressure variability in patients with obstructive sleep apnea

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Study Objectives: Cardiovascular comorbidities in obstructive sleep apnea (OSA) are difficult to treat, perhaps due to autonomic dysfunction. We assessed beat-to-beat blood pressure (BP) variability (BPV) in OSA while considering other markers derived from electrocardiogram and continuous BP signals.

Methods: We studied 66 participants (33 participants with OSA: respiratory event index [mean ± SEM]: 21.1 ± 2.7 events/h; 12 females, aged 51.5 ± 2.4 years; body mass index: 32.8 ± 1.4 kg/m^2; 33 healthy controls: 20 females; aged 45.3 ± 2.4 years; body mass index: 26.3 ± 0.7 kg/m^2). We collected 5-minute resting noninvasive beat-to-beat BP and electrocardiogram values. From BP, we derived systolic, diastolic, and mean BP values, and calculated variability as standard deviations (systolic BPV, diastolic BPV, BPV). We also calculated diastole-to-systole time (time to peak). From the electrocardiogram, we derived QRS markers and calculated heart rate and heart rate variability. We performed a multivariate analysis of variance based on sex and group (OSA vs control), with Bonferroni-corrected post hoc comparisons ($P \leq .05$) between groups. We calculated correlations of BPV with biological variables.

Results: Multivariate analysis of variance showed effects of diastolic BPV and BPV in OSA; post hoc comparisons revealed high diastolic BPV and BPV only in female participants with OSA vs controls. QRS duration was higher in OSA, with post hoc comparisons showing the effect only in males. BPV correlated positively with heart rate variability in controls but not in participants with OSA. BPV correlated positively with time to peak in females with OSA and OSA combined, whereas there was no BPV–time-to-peak correlation in healthy participants.

Conclusions: The findings show sex-specific autonomic dysfunction reflected in beat-to-beat BP in OSA. The higher BPV may reflect poor baroreflex control or vascular damage in OSA, which are potential precursors to cardiovascular complications.

Keywords: sleep-disordered breathing, baroreflex, autonomic nervous system, cardiovascular disease

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Obstructive sleep apnea is accompanied by disrupted autonomic function, which likely contributes to the difficulty in treating cardiovascular comorbidities of the sleep disorder. Such disruption may be reflected in poorly regulated blood pressure, which we sought to assess using a noninvasive measure of beat-to-beat variability of blood pressure.

Study Impact: The findings showed increased blood pressure variability in obstructive sleep apnea distinct from other cardiovascular measures, reflecting less-effective blood pressure control than in healthy people. Furthermore, separation by sex showed differences between men and women, consistent with other studies that show sex-specific influence of obstructive sleep apnea on autonomic functions.

INTRODUCTION

Obstructive sleep apnea (OSA) is a prominent risk factor for hypertension and other cardiovascular disease (CVD).[1] Furthermore, CVD in OSA is difficult to treat,[2] possibly due to underlying autonomic nervous system dysfunction, as reflected, for example, by persistently elevated sympathetic tone during waking.[3,4] Patients with OSA also show waking differences in blood pressure (BP) fluctuations and heart rate (HR) responses to autonomic challenges, compared with healthy people.[3,5] Such challenges are associated with altered brain functional responses in the brainstem and higher regions of the central autonomic network (insula, ventromedial prefrontal cortex, anterior cingulate cortex, and cerebellum, and brainstem regions including dorsal pons and rostral ventrolateral medulla).[6–9] The altered neural responses revealed by dynamic challenges suggest these brain regions may also show altered function in the resting state, potentially contributing to the observed reduced baroreceptor reflex,[10] altered HR variability (HRV),[11–13] and the aforementioned high sympathetic tone.[3,4] We earlier showed brainstem changes associated with resting alterations in muscle sympathetic nerve activity in OSA.[7,14] Peripherally, autonomic disruption is closely associated with endothelial dysfunction in OSA,[4,15,16] so the source of autonomic disruption likely in OSA has multiple sources. Our goal was to better understand the autonomic disruption in OSA as observable through peripheral measures. Specifically, beat-to-beat BP variability (BPV) and HRV measures are relatively simple, low cost, and noninvasive, but while several studies have assessed HRV in OSA, BPV is less well characterized.[17]

There are various sources of autonomic abnormalities associated with OSA[18] and some of these appear to resolve with

continuous positive airway pressure (CPAP) treatment, whereas others do not. While these differences have been well documented, it remains unknown why they exist or even which contribute to CVD in OSA. Higher sympathetic activation measured by muscle sympathetic nerve activity (which is centrally driven) occurs in OSA during both wakeful rest and sleep,[18,19] and CPAP treatment reduces both the elevated waking muscle sympathetic nerve activity[14,20–23] and the elevated nocturnal epinephrine (a measure of sympathetic activation).[24] This reduction in sympathetic activity with CPAP is not correlated to BP dipping (which is reduced in people with sympathetic activation).[24] Additionally, it has been suggested that, in normotensive patients with OSA, sympathetic nervous system activity, based on norepinephrine excretion, is continuously increased and is not affected by short-term CPAP treatment.[24] It appears that, with CPAP treatment, some peripheral autonomic disruption stays and this is most obvious with lower-severity OSA.

It is thought that intermittent hypoxia, poor tissue oxygenation, and perfusion in OSA can lead to peripheral changes such as endothelial dysfunction.[4,18,25,26] Endothelial dysfunction, a term that encompasses nitric oxide production, platelet activity, and other molecular functions that regulate blood flow and BP, may be present years prior to CVD.[27,28] Poor vascular homeostasis and poor vascular smooth muscle function are likely reflected as improper blood flow regulation,[25] and these blood flow patterns are predictive of the development of atherosclerosis and cardiovascular disease.[25,29] We can obtain measures reflecting blood flow regulation by the autonomic nervous system as HRV from a continuous electrocardiogram (ECG).[17,30–34] HRV can be calculated as power in frequency bands, and a ratio of low frequency power termed sympathetic-to-vagal ratio is an indirect measure of sympathetic activation.[35,36] However, while HRV is widely used and simply interpreted, there are limitations, which are well addressed in the literature.[37–40] Interpretations as sympathetic or parasympathetic activity are mostly accurate "under normal conditions," and individual variation in HR, medication usage, and cardiovascular or neural pathologies can influence HRV measures separately from autonomic nervous system function.[40] The potential limitations of HRV are one reason alternative measures of autonomic status are useful, and part of our rationale for assessing BPV.[41,42]

While noninvasive BPV is not as simple to acquire as HRV, moment-to-moment changes in BP are the triggering events for baroreflex regulation that lead to moment-to-moment HR changes, so BPV measures can be seen as complementary to HRV measures.[42] Higher BPV has been found in both sleep and wakefulness in untreated OSA.[5,43] Since BP homeostasis at rest is maintained by the baroreflex circuit, higher BPV reflects poorer baroreflex control. In OSA, it is also possible that the demand on the baroreflex system is increased by vascular pathology due to vessel elasticity changes and endothelial dysfunction.[44] A signal measure to evaluate BPV, continuous noninvasive arterial pressure (CNAP), allows for other variables to be assessed. Time to peak (TTPK), the time interval between diastolic BP (DBP) and systolic BP (SBP), or systolic upstroke time, is derived from radial pressure waveform and is known to be higher in peripheral artery endothelial diseases.[45] TTPK is also known to be higher in aortic stenosis[46] and could potentially be an indicator of cardiovascular problems in OSA. Other cardiovascular characteristics that can be measured from CNAP or ECG signals are used to assess autonomic status. These include cardiac output (CO), an index of blood flow through the heart that is related to BP and HR,[47] and which is linked with sympathetic tone and baroreflex action in healthy people.[48] Another ECG characteristic is QRS duration, which reflects time of ventricular depolarization,[49] and which is associated with cardiac abnormalities and development of CVD.[50] A simple time-domain measure of HRV is the standard deviation of RR intervals. Finally, resting HR is both a potential confounder and a marker in and of itself.[40]

The objective of this study was to use CNAP and ECG to assess the above-mentioned variables of autonomic regulation in OSA. Both clinical variables and autonomic measures show substantial male–female differences in OSA,[51–54] so we included sex-specific assessment. We hypothesized that untreated OSA is associated with higher BPV, higher TTPK, and high sympathetic-to-vagal ratio, and that these changes differ in males and females. We hypothesized that the higher BPV in OSA is, to some degree, independent of other BP- and ECG-derived metrics of cardiac function. We included other metrics of cardiovascular function based on CNAP and ECG signals that reflect aspects of autonomic status, including mean BP (MBP), CO, HR and time-domain HRV, and QRS duration. We predicted that, when compared with a healthy group, OSA would be associated with higher BP and HR,[55] no difference in resting CO (since CO differences mainly appear acutely[56]), higher time-domain HRV,[57] and longer QRS duration.[58]

METHODS

We studied 33 untreated participants with OSA and 33 healthy control participants. All participants were recruited via fliers posted at University of California, Los Angeles (UCLA), and the Los Angeles area. Fliers for potential participants with OSA targeted people with confirmed or suspected OSA, and separate fliers for control participants targeted healthy people. Participants in the OSA group had the sleep disorder diagnosed by the UCLA Sleep Disorders Center. Participants without a recent diagnosis (<6 months) or with suspected OSA were referred for a 2-night home sleep apnea test with an Apnea Risk Evaluation System (ARES) device.[59] The Apnea Risk Evaluation System (ARES) has FP1 and FP2 for deriving electroencephalogram, electro-oculography, and electromyography values but it does not qualify for the American Academy of Sleep Medicine definition of home sleep apnea test sleep vs wake, and the respiratory event index as opposed to the apnea-hypopnea index is calculated. These home sleep apnea test limitations mean the sleep characteristics are not as reliable as those obtained in-clinic, although there are no concerns about diagnosing OSA. The Apnea Risk Evaluation System (ARES) device captures airflow using a nasal cannula and pressure transducer, and apnea is cessation (>90% reduction) in flow for ≥10 seconds and hypopnea is ≥50% reduction in flow for ≥10 seconds. The

criteria are for respiratory event index apneas and hypopneas of 4% desaturation, consistent with the 2012 American Academy of Sleep Medicine scoring criteria.[60] The scoring assigned to participants was based on the average over the single night with the longest valid recording time. The participants with OSA 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 ± standard deviation time difference between physiology and sleep study = 25.1 ± 26.6 days), the group included people who had been offered but did not use CPAP. Control 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 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 the home sleep apnea test through the UCLA Sleep Disorders Center to ensure the lack of OSA or other sleep disorders. Thirteen people in the control group had such sleep studies. Participants with OSA also completed the online questionnaire. 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, and β-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 midmorning (9:30 AM, earliest) to early evening (6:30 PM, latest start). The protocol timeline is illustrated in **Figure 1**. During the initial steps including a cuff BP recording, participants were seated at a desk without back support; during the continuous physiology recording, they were seated in a chair with back support. The 5-minute resting physiology was recorded (green box in **Figure 1**) after a 90-second stabilization period, which was preceded by approximately 1 hour of a series of procedures that were consistent across all participants. Continuous data were collected with BIOPAC's AcqKnowledge MP150 system (BIOPAC Systems, Inc; Goleta, CA). We obtained ECG, beat-to-beat CNAP (CNAP Monitor 500; CNSystems Medizintechnik GmbH, Berlin, Germany), and breathing movements from a respiration belt (BIOPAC). The CNAP monitor is based on pulse pressure at the finger and is calibrated with an automatically obtained brachial cuff measure ("CNAP initialization" in **Figure 1**). In brief, at initialization, the CNAP signal is matched to brachial cuff values, thus ensuring the signal derived from the pulse pressure at the finger is matched to a standard measure. The CNAP automated cuff values are not available. We used the CNAP v3.5 protocol with adult default settings (https://www.biopac.com/wp-content/uploads/nibp100d_cnap_monitor.pdf).[61] The filter setting on the CNAP acquisition was 5 kHz low pass. All data were sampled at 1 kHz.

Physiological metrics were derived from the raw signals recorded during the 5 minutes of rest (**Figure 1**). While HRV can be calculated with shorter periods,[62,63] we aimed to use 5 minutes for BPV, and therefore for consistency used the same data period for all measures. It is noteworthy that this "resting state" is likely to have varied across participants, as we anecdotally observed variations in participants' emotional responses (some people found "resting" for 5 minutes stressful), which would potentially influence the physiological state.[63,64] The continuous BP was used to calculate TTPK, CO, SBP, DBP, and MBP. The CO estimation used the pulse contour analysis method, which has limited reliability in people with severely compromised cardiovascular function, but which is otherwise a moderately valid noninvasive estimation.[65] We measured BPV as the standard deviations of MBP (BPV), SBP (systolic BPV), and DBP (diastolic BPV). From the ECG, we calculated HR based on the RR interval (RR-I). HRV measure in the frequency domain included sympathetic to vagal balance ratio (low frequency [0.04–0.15 Hz] by high frequency [0.15–0.4 Hz] power), and HRV in the time domain included RR-I variability (standard deviation of RR intervals).[35]

Only signals that did not have artifact or missing data were analyzed due to the sensitivity of HRV calculations to such errors.[62] Initial processing was done in AcqKnowledge 5. Only participants with 5 minutes of valid data after processing were included in the analysis. The first step was visual inspection and artifact rejection or correction of the ECG and BP signals. Any flat or noisy signal that lasted for more than 0.1 seconds was considered missing data and that recording was excluded. Momentary noise (<0.1-second spike, trough, noise) was removed and replaced with linearly interpolated signals unless the spike occurred at the time of an *R*-wave. We bandpass filtered the BP signal at 60 Hz to any line noise. As a first pass, automatic peak and trough detection was performed in AcqKnowledge on the BP signal, and automatic QRS detection identified ECG waveform characteristics. We used the arterial BP classifier from the "Hemodynamic" routine to identify systole and diastole markers and "Analysis find cycle" routine in AcqKnowledge and the voltage thresholding technique to generate the QRS. Each automatically detected event was manually checked and corrected as needed. Approximately 5% of recordings had artifacts that precluded inclusion. We used AcqKnowledge to perform the HRV frequency and time-domain calculations and exported the measures to Excel.

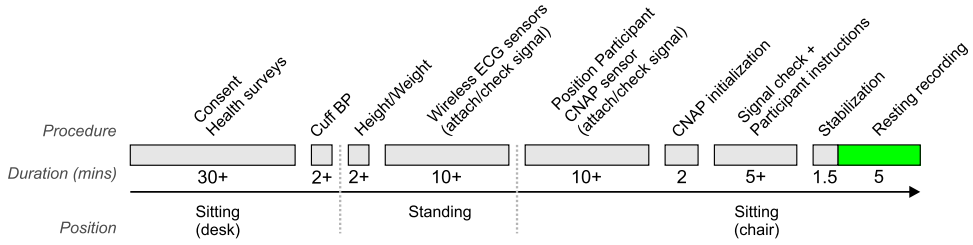
Our analysis pipeline uses several software packages based on ease of use, available calculations, and visualization options. Descriptive statistics and independent-samples *t* tests between OSA and control means were calculated for all variables in Microsoft Excel. We used MATLAB's (The Mathworks, Inc; Natick, MA) "boxplot" to visualize measures by group; this function displays median, lower, and upper quartiles; range without outliers; and outliers defined as values either 1.5 times the interquartile range above the upper quartile or below the lower quartile. Multivariate analysis of variance was performed in

Table 1—Participant characteristics.

	All			Females			Males		
	Control (n = 33)	OSA (n = 33)	*P*[a]	Control (n = 20)	OSA (n = 12)	*P*[a]	Control (n = 13)	OSA (n = 21)	*P*[a]
Age, years	45.3 ± 13.6 [23.0–67.0]	51.5 ± 14.0 [25.0–77.0]	*.02*	44.7 ± 13.0 [24.0–66.0]	51.7 ± 6.8 [34.0–77.0]	*.02*	46.3 ± 14.9 [23.0–67.0]	48.7 ± 13.7 [25.0–77.0]	.64
BMI, kg/m^2	26.3 ± 4.3 [19.8–37.6]	32.8 ± 8.0 [21.9–54.3]	*<.001*	25.7 ± 4.7 [19.8–37.6]	32.7 ± 9.3 [21.9–54.3]	*.01*	27.2 ± 3.6 [21.8–33.2]	32.8 ± 7.4 [22.2–47.1]	*.01*
Systolic BP, mm Hg	117.1 ± 17.2 [89.0–159.0]	129.1 ± 17.3 [99.0–159.0]	*.007*	111.6 ± 16.4 [89.0–145.0]	130.6 ± 17.2 [105.0–159.0]	*.005*	125.5 ± 15.5 [107.0–159.0]	128.2 ± 17.7 [99.0–156.0]	.64
Diastolic BP, mm Hg	77.9 ± 11.9 [53.0–97.0]	83.7 ± 10.0 [61.0–106.0]	*.039*	76.8 ± 9.4 [59.0–92.0]	83.82 ± 7.89 [72.0–94.0]	*.044*	79.7 ± 15.2 [53.0–97.0]	83.7 ± 11.2 [61.0–106.0]	.39
Mean arterial BP, mm Hg	91.0 ± 12.0 [70.3–117.7]	98.9 ± 11.7 [73.7–117.3]	*.002*	88.4 ± 10.7 [70.3–106.7]	99.4 ± 10.2 [83.7–112.3]	*.009*	94.9 ± 13.2 [77.0–117.7]	98.5 ± 12.6 [73.7–117.3]	.44
Sleep parameters									
REI, events/h	n/a	21.1 ± 15.3 [6.0–67.4]	n/a	n/a	24.7 ± 21.3 [6.9–67.4]	n/a	n/a	19.1 ± 10.7 [6.0–42.0]	n/a
Minimum SaO_2, %	n/a	83.6 ± 5.8 [68.8–92.0]	n/a	n/a	83.3 ± 6.5 [70.9–92.0]	n/a	n/a	83.8 ± 5.5 [68.8–92.0]	n/a
Baseline SaO_2, %	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

Characteristics of participants with OSA and control participants, separated by sex. Data are presented as means ± standard deviations [range]. Group differences were assessed with independent-samples *t* tests. All *P* values ≤ .05 are italicized. BMI = body mass index; BP = blood pressure; n/a = not applicable; OSA = obstructive sleep apnea; REI = respiratory event index; $Sa0_2$ = oxygen saturation. [a]*P* for *t* test, group comparison OSA vs control.

Figure 1—Protocol timeline.



Sequence, participant position, and duration of procedures. Green indicates the 5-minute-rest recording period. Participants had back support in a "chair" but not at a "desk." BP = blood pressure; CNAP = continuous noninvasive arterial pressure; ECG = electrocardiogram.

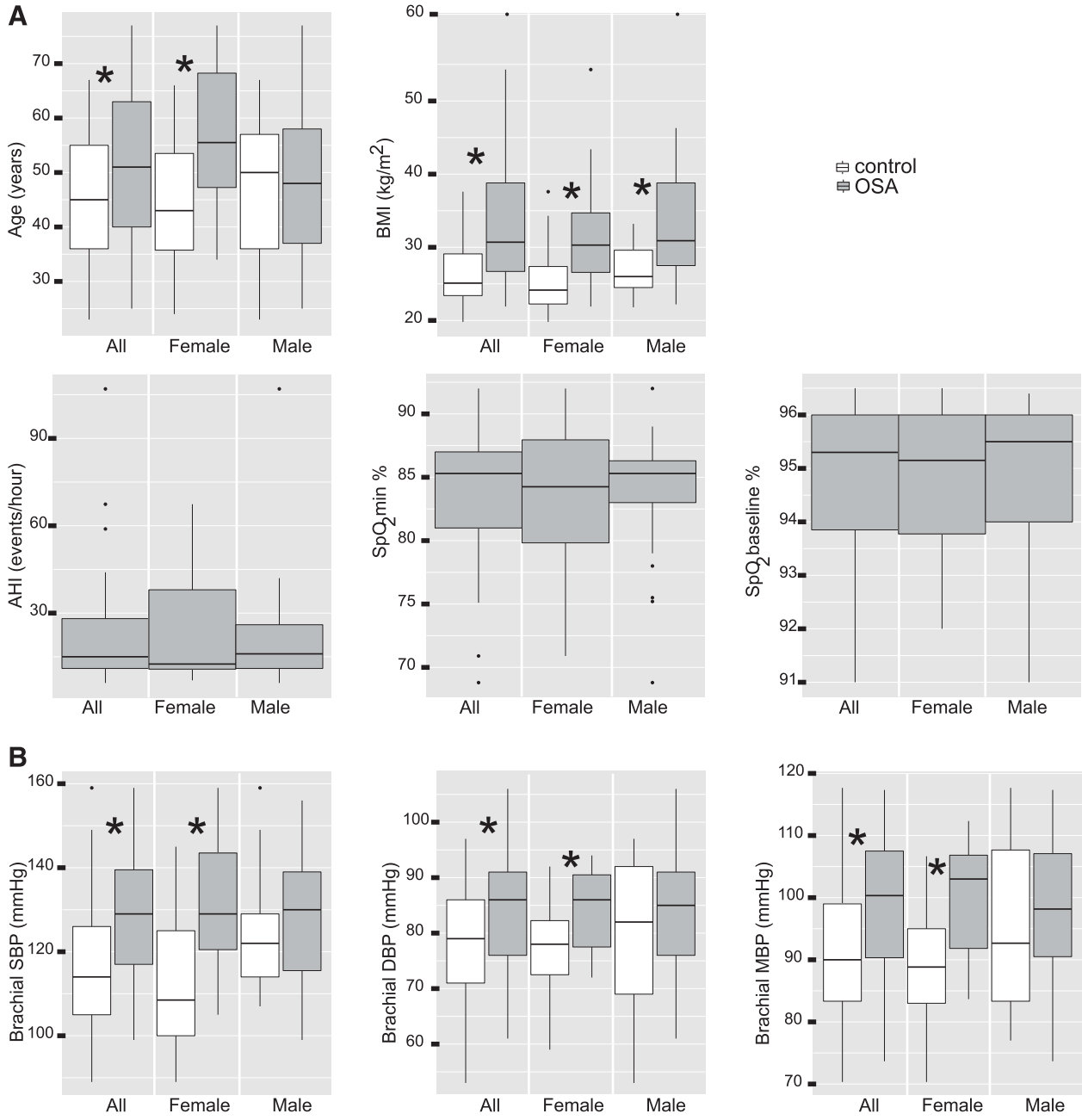
IBM (R) SPSS v26 (IBM Corporation, Armonk, NY), assessing the physiological metrics as a function of group with sex as a factor. Post hoc assessments of individual variables were conducted with Bonferroni correction at $P \leq .05$. Analyses were repeated with female and male groups separately. Pearson's *R* correlation coefficients were calculated with MATLAB 9.6, which also allows visualizations in scatterplots. We correlated BPV with age, body mass index, brachial BP, and the physiological measures of HR, QRS duration, RR-I variable, sympathetic-to-vagal balance obtained with ECG and with BP and TTPK. We tested for independence by assessing significance of correlations. To consider relationships without influence from outliers, we recalculated the correlations after removing BPV values greater than 2 standard deviations from the mean.

Power analyses were performed for multivariate analysis of variance with G*Power 3.1.[66] The original design called for 80 participants in order to detect a medium–large standardized effect size (Cohen's f2 ≈ 0.25) at an α of 0.05 and power of 0.8 with 2 groups and 12 response variables. This calculation is conservative as the 12 response variables include closely correlated measures (MBP, SBP, DBP; and BPV, systolic BPV, diastolic BPV). Data collection was discontinued before the target sample was reached due to the onset of the 2020 pandemic; and after excluding artifactual recordings, the resulting power was $f^2 = 0.32$ (by convention, a "moderate-to-large" standardized effect size).[67]

RESULTS

Participant characteristics are shown by group in **Table 1** and **Figure 2A**. Body mass index was higher in participants with OSA than in controls. The OSA group was older than the control group, mainly due to older female participants with OSA. Similarly, the female OSA group showed a higher proportion of

Figure 2—Box plots of demographics and biomarkers.

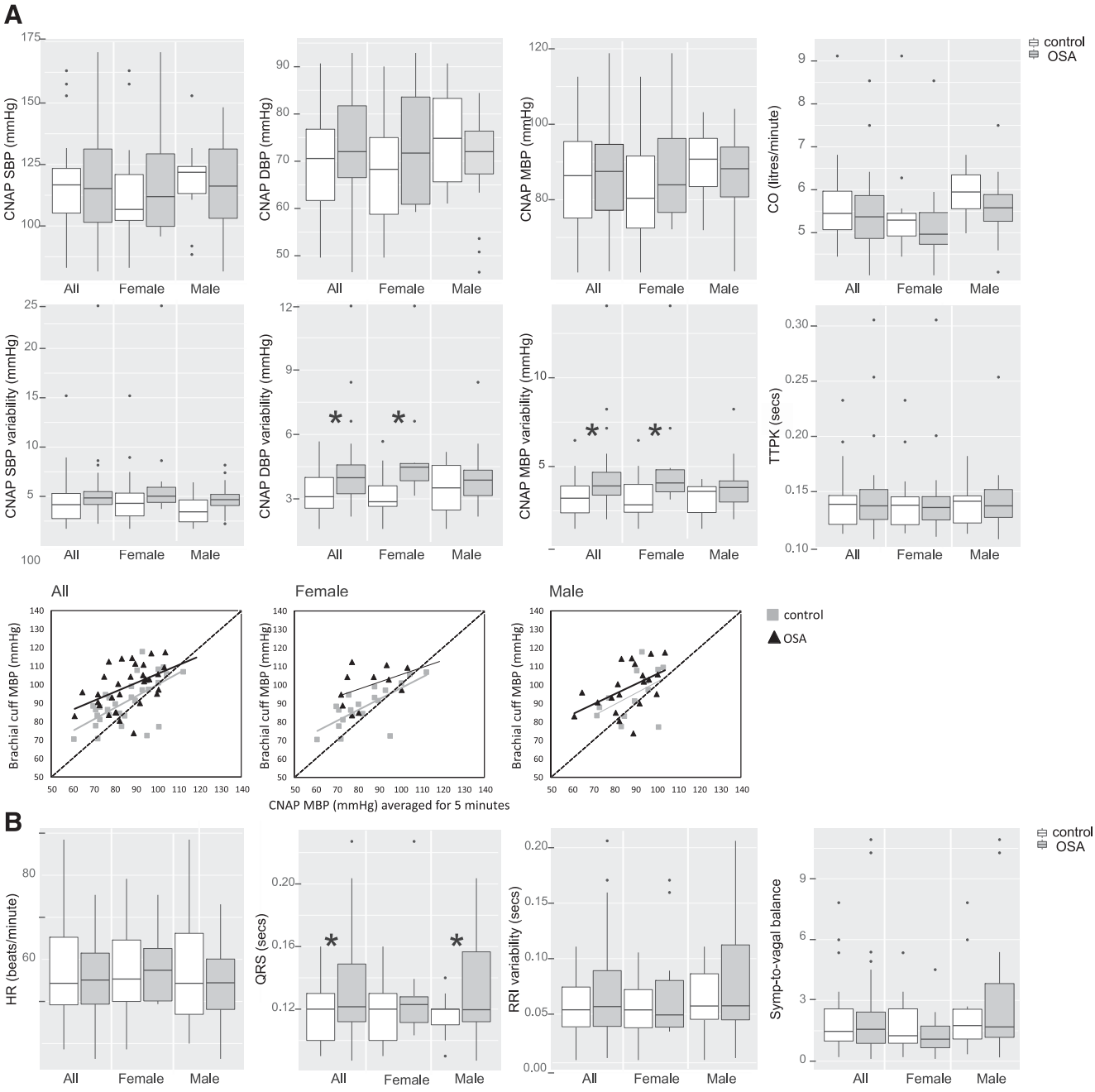


Box plots indicating median, interquartile range, range, and outliers (see Methods). Demographic and biomarkers from Table 1 for OSA and control in the combined-sex population and separately in males and in females. *Significant OSA vs control difference by *t* test. **(A)** Age, BMI, and OSA sleep parameters. **(B)** Brachial BP measures. AHI = apnea-hypopnea index; BMI = body mass index; BP = blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure; OSA = obstructive sleep apnea; SBP = systolic blood pressure; SpO_2 = saturation of oxygen obtained from pulse oximeter.

postmenopausal women, with 50% vs 25% for control (perimenopause: OSA, 8%; control, 10%; premenopause: OSA, 42%; control, 65%). Within the OSA group, males and females had similar sleep parameters. With respect to BP, we found that 6% of controls (2 females) and 12% of participants with OSA (2 males and 2 females) reported hypertension, SBP ≥140 mm Hg. Measurements from the brachial cuff had greater SBP, DBP, and MBP in the OSA group than in the control group. These differences were driven primarily by the female participants with OSA who had higher BP values than female controls, while male participants with OSA had values similar to male controls (Figure 2B).

The average resting BP derived from 5 minutes of continuously recorded data did not show significant differences between OSA and control groups (Figure 3 and Table 2). There were no differences when groups were divided based on sex. MBP measurements from the one-off brachial reading and 5-minute average of CNAP were correlated in control females ($R = .73$, $P < .001$) and males with OSA ($R = .49$, $P < .05$), with

Figure 3—Physiological variables.



Box plots indicating median, interquartile range, range, and outliers (see Methods). **(A)** BPV, BP, CO, and TTPK obtained from the continuous BP. MBP obtained from the brachial cuff (*y* axis) and the average MBP from 5 minutes of CNAP (*x* axis) are shown. **(B)** HR, QRS duration and HRV, and sympathetic-to-vagal balance from the ECG are shown. *Significant OSA vs control difference in the MANOVA model (refer to Table 2). Regression lines in **A** are thick for significant correlations. BP = blood pressure; BPV = mean arterial blood pressure variability; CNAP = continuous noninvasive arterial pressure; CO = cardiac output; DBP = diastolic blood pressure; ECG = electrocardiogram; HR = heart rate; HRV = heart rate variability; MBP = mean arterial blood pressure; OSA = obstructive sleep apnea; RRI = RR interval; SBP = systolic blood pressure; TTPK = time to peak.

weaker, nonsignificant correlations in control males (R = .48, P = .09) and females with OSA (R = .44, P = .18).

The multivariate analysis of variance model results are displayed in Table 2 and Figure 3. There were no significant effects of SBP, DBP, MBP, or systolic BPV; however, diastolic BPV and BPV were higher in participants with OSA compared with controls. This increase in BPV in participants with OSA was driven by female participants with OSA who displayed increased mean BPV of 1.8 mm Hg/beat and systolic BPV of 1.8 mm Hg/beat compared with only 0.6 mm Hg/beat and 0.7 mm Hg/beat in male participants with OSA. No differences occurred between participants with OSA and control participants in systolic BPV. In addition, while there were no significant differences between groups in HR, CO, TTPK, RR-I

Table 2—MANOVA results for OSA vs control groups.

	All		Females		Males	
	OSA − Control	P^a	OSA − Control	P^a	OSA − Control	P^a
SBP, mm Hg	−0.02 ± 5.00	.99	2.95 ± 7.11	.68	−2.99 ± 7.04	.67
DBP, mm Hg	0.66 ± 2.92	.82	5.25 ± 4.15	.21	0.56 ± 0.55	.31
MBP, mm Hg	0.43 ± 3.32	.89	4.49 ± 4.72	.35	−3.62 ± 4.67	.44
SBPV, mm Hg	1.43 ± 0.79	.07	1.85 ± 1.15	.11	0.93 ± 1.14	.42
DBPV, mm Hg	1.14 ± 0.38	*.004*	1.81 ± 0.55	*.002*	0.56 ± 0.55	.31
BPV, mm Hg	1.25 ± 0.43	*.005*	1.78 ± 0.62	*.005*	0.72 ± 0.62	.24
TTPK, seconds	0.01 ± 0.01	.43	0.01 ± 0.01	.36	0.00 ± 0.01	.85
CO, liters/minute	−0.18 ± 0.23	.42	−0.11 ± 0.32	.73	−0.26 ± 0.32	.42
HR, beats/minute	−0.74 ± 2.77	.731	1.51 ± 4.06	.71	−3.48 ± 4.02	.39
QRS duration, seconds	0.015 ± 0.007	*.016*	0.011 ± 0.010	.21	0.020 ± 0.009	*.027*
Sympathetic to vagal ratio	0.05 ± 0.55	.92	−0.19 ± 0.79	.81	0.29 ± 0.78	.71
RR-I variability, seconds	0.02 ± 0.01	.12	0.01 ± 0.01	.35	0.02 ± .015	.21

Data are presented as adjusted mean group difference ± SEM for dependent physiological variables, with separation by sex. The overall model was significant ($P < .05$). All P values ≤ .05 are italicized. BPV = mean arterial blood pressure variability; CO = cardiac output; DBP = diastolic blood pressure; DBPV = diastolic blood pressure variability; HR = heart rate; MANOVA = multivariate analysis of variance; MBP = mean arterial blood pressure; OSA = obstructive sleep apnea; RR-I, RR interval; SBP = systolic blood pressure; SBPV = systolic blood pressure variability; TTPK = time to peak. [a]P for MANOVA, group comparison OSA vs control.

variability, or sympathetic to vagal ratio, QRS duration was 20 milliseconds longer in participants with OSA than controls. This increase in QRS duration in OSA was driven by male participants with OSA who displayed significantly longer (by 0.02 seconds) QRS duration than control males; in contrast, female participants with OSA also displayed longer QRS (by 0.01 seconds) compared with control female participants but the difference was not significant.

The correlations of BPV to other demographic and physiological variables in participants with OSA and controls are shown in **Table 3** and **Figure 4**. BPV correlated positively (R = .59) with TTPK in the combined male–female OSA group but there were no significant correlations in the control group. BPV correlated positively (R = .79) with TTPK in the female OSA group but there were no significant correlations in the female control group. In males, there were no significant TTPK–BPV correlations. BPV correlated differently with CO in participants with OSA and controls. BPV correlated positively with HRV in time-domain (RR-I variability) in controls (R = .5) but not in participants with OSA. There were no correlations between BPV and HR, or with BPV and HRV in frequency domain (sympathetic to vagal balance), or with BPV and QRS duration. Significant group differences in correlations with MBP were observed in TTPK (all and females), brachial MBP (females), and RR-I variability (all). Higher BPV in females with OSA correlated negatively to the MBP obtained from the brachial cuff (R = −.68), but not in control females or either OSA or control male groups. However, BPV did not correlate with the average MBP. Outliers defined as BPV greater than 2 standard deviations from the mean included 1 female and 1 male participant with OSA. Removing these participants affected the magnitude of some correlations (**Table 3**) and eliminated significant TTPK-BPV effects but added significant effects for RR-variability-BPV in females and HR-BPV in males. The significance of OSA–control differences in correlations remained unaltered with the exception of CO-BPV in the combined female and male groups (**Table 3**).

DISCUSSION

People with OSA showed higher BPV and longer QRS compared with control participants. The BPV showed only moderate or nonsignificant correlations with other BP and ECG-derived metrics including HR, HRV, and MBP. Separating by sex showed that females with OSA had significantly higher BPV, whereas the QRS duration was significantly higher in males. The BPV findings provide further evidence of autonomic dysregulation in OSA, broadly replicating earlier findings.[5] The moment-to-moment variability in BP reflects a distinct physiologic process not captured by classic BP measures, and BPV is a potential marker of autonomic control obtainable noninvasively.

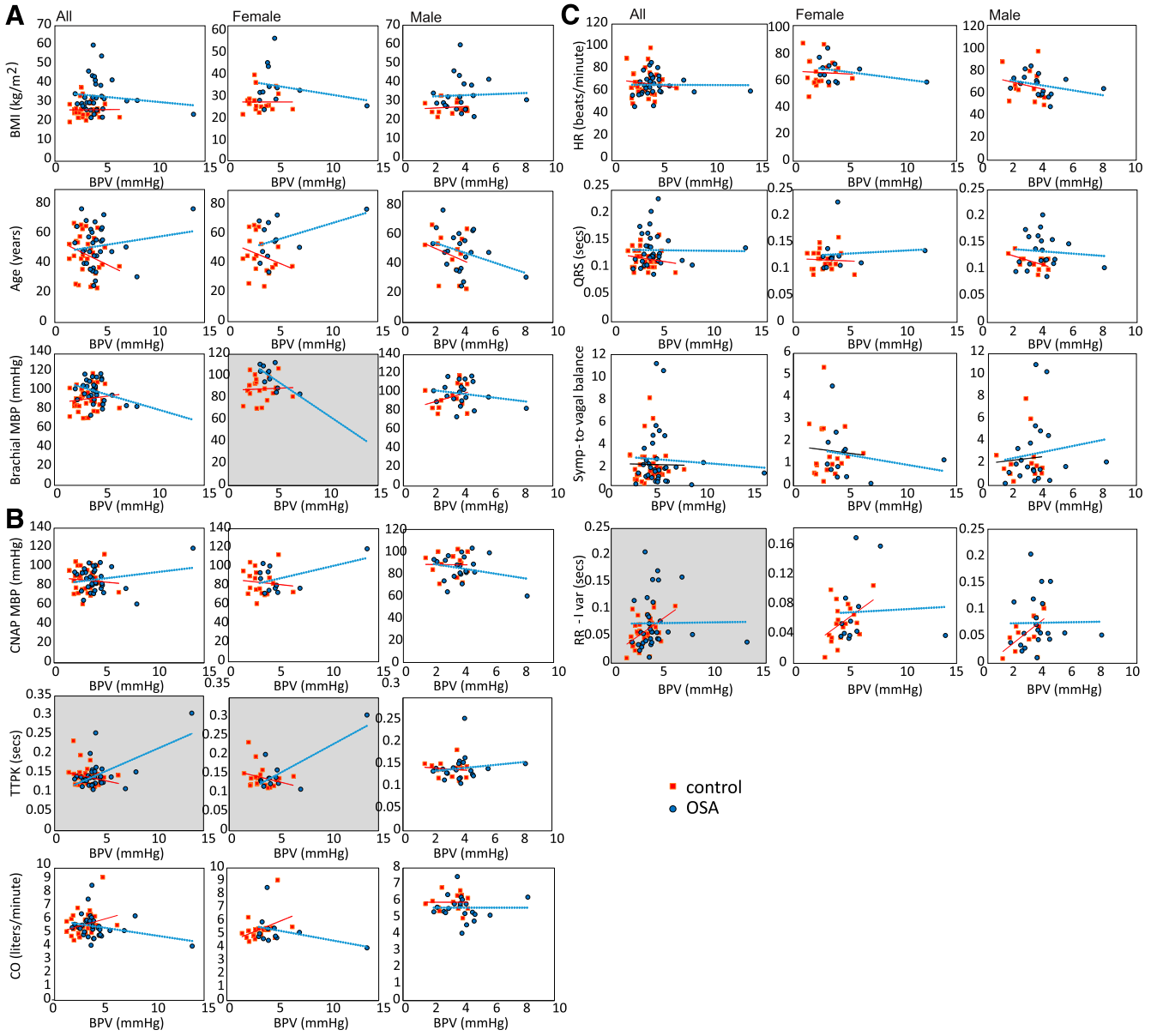
The altered BPV in OSA likely reflects several pathophysiological processes both centrally and peripherally mediated. More variable BP suggests altered baroreflex control, as seen in populations with OSA generally[68–70] and in acute responses to intermittent hypoxia.[71] However, BPV during 5 minutes of rest is not a direct measure of baroreflex sensitivity. In earlier studies, patients with OSA showed an impairment of endothelium-dependent vasodilation,[72] which could arise directly from chronic intermittent hypoxia or from OSA comorbidities such as obesity, insulin resistance, and hypertension.[73–75] We found that the increases in BPV in OSA were driven by changes in females, which may reflect a sex-specific vulnerability. However, the small number of female participants with OSA means that the finding of high BPV has limited generalizability.

Table 3—Correlations of BPV with other variables.

	All					Female					Male				
	Control (n = 33)		OSA (n = 33; No Outliers, n = 31)		OSA vs Control	Control (n = 20)		OSA (n = 12; No Outliers, n = 11)		OSA vs Control	Control (n = 13)		OSA (n = 21; No Outliers, n = 20)		OSA vs Control
	R	*P*[a]	*R*	*P*[a]	*P*[b]	*R*	*P*[a]	*R*	*P*[a]	*P*[b]	*R*	*P*[a]	*R*	*P*[a]	*P*[b]
Demographic and MBP variables															
Age, years	−.27	.13	.16 (−.35)	.38 (.85)	.09 (.77)	−.27	.26	.45 (.03)	.14 (.92)	.06 (.47)	−.28	.35	−.33 (−.17)	.14 (.46)	.89 (.77)
BMI, kg/m^2	.01	.93	−.15 (.14)	.52 (.44)	.62 (.89)	−.00	.99	−.24 (.13)	.46 (.71)	.56 (.76)	.09	.76	−.04 (.15)	.87 (.53)	.89 (.89)
Brachial MBP, mm Hg	.13	.49	−.33 (−.23)	.07 (.23)	.07 (.41)	.04	.86	−.68 (−.68)	*.02* (*.02*)	*<.05* (*.04*)	.32	.28	−.21 (.016)	.38 (.95)	.16 (.42)
Physiological variables (5 minutes)															
Mean CNAP MBP, mm Hg	.02	.92	.21 (−.09)	.24 (.62)	.42 (.56)	−.10	.68	.49 (−.45)	.1 (.17)	.12 (.38)	−.02	.95	−.25 (.21)	.28 (.38)	.55 (.56)
TTPK, seconds	−.24	.19	.59 (−.035)	*<.001* (.85)	*<.001* (.52)	−.27	.25	.79 (−.31)	*<.01* (.35)	*<.001* (.92)	−.12	.69	.15 (.14)	.52 (.57)	.49 (.52)
CO, liters/minute	.28	.12	−.27 (−.05)	.13 (.78)	*<.05* (.52)	.39	.1	−.36 (−.09)	.25 (.78)	.06 (.24)	.01	.97	.00 (−.24)	.99 (.31)	.98 (.52)
Mean HR, beats/minute	−.10	.56	−.01 (−.19)	.95 (.32)	.72 (.08)	−.05	.85	−.35 (−.17)	.26 (.61)	.43 (.77)	−.20	.51	.21 (.46)	.36 (*.04*)	.29 (.08)
QRS duration, seconds	−.18	.33	−.01 (.063)	.94 (.64)	.52 (.07)	−.05	.82	.09 (.07)	.79 (.84)	.73 (.80)	−.53	*<.05*	−.09 (.12)	.71 (.61)	.15 (.07)
Sympathetic to vagal ratio	−.01	.95	−.06 (.024)	.73 (.90)	.88 (.62)	−.07	.79	−.21 (−.41)	.52 (.21)	.73 (.39)	.08	.80	.13 (.27)	.57 (.25)	.88 (.62)
RR-I variability, seconds	.50	*<.01*	.01 (.32)	.95 (.08)	.07 (.15)	.46	*<.05*	.05 (.70)	.88 (*.02*)	.28 (.44)	.62	*<.05*	.01 (.14)	.95 (.56)	.07 (.15)

Pearson's *R* correlation values between BPV and all other variables, for OSA and control separated by sex. The significance levels of individual correlations are presented, along with OSA vs control comparisons. All *P* values ≤ .05 are italicized. Correlations were repeated with outliers removed. Outliers are defined as >2 standard deviations from the mean. Values in parenthesis indicate that outliers were removed. BMI = body mass index; BPV = mean arterial blood pressure variability; CO = cardiac output; CNAP = continuous noninvasive arterial pressure; HR = heart rate; MBP = mean arterial blood pressure; OSA = obstructive sleep apnea; RR-I, RR interval; TTPK = time to peak. [a]*P* for Pearson's R (correlation of variables with BPV). [b]*P* for group comparison of Pearson's *R* between OSA and control.

Figure 4—Scatterplots of BPV with demographic and biological measures.



BPV plotted against **(A)** age, BMI, brachial MBP; **(B)** averaged BP and TTPK, CO; **(C)** heart rate, QRS duration, HRV (sympathetic to vagal balance, RR-I variability). The regressions in each group of OSA (in blue) or control (in red) are shown as solid where significant. Correlations significantly different between OSA and control groups are highlighted in gray. The correlation results are shown in **Table 3**. BMI = body mass index; BP = blood pressure; BPV = mean arterial blood pressure variability; CNAP = continuous noninvasive arterial pressure; CO = cardiac output; HR = heart rate; HRV = heart rate variability; MBP = mean arterial blood pressure; OSA = obstructive sleep apnea; QRS = QRS duration; +RR-I var = RR interval variability; Symp = sympathetic; TTPK = time to peak.

Similar to previous studies in which male and female participants were combined, we found that OSA was associated with increased QRS duration.[58,76] In this sample, the increased QRS interval was derived principally from male participants with OSA. Previous studies have shown that OSA is associated with changes in cardiac structure such as left ventricular hypertrophy.[77,78] Longer QRS duration is an independent predictor of sudden cardiac death[79] and mortality[80] in individuals with hypertension and heart failure, 2 conditions commonly associated with OSA. Our finding that QRS duration is particularly altered in male participants with OSA raises the possibility that males may be particularly sensitive to cardiac remodeling associated with OSA. Limited supporting evidence includes higher levels of high-sensitivity troponin T in males with OSA, a biomarker of subclinical myocardial injury.[81] However, the same study reported that greater OSA severity was more strongly positively associated with higher high-sensitivity troponin T in women than in men, and that after a 13-year follow-up, OSA severity was associated with incident heart failure in women but not men. Additionally, OSA assessed in midlife was significantly associated with left ventricular hypertrophy in women but not men.[81] Therefore, the greater QRS duration observed here may not generalize to the general male OSA population.

The slightly older control group may have influenced the findings. In hypertensive participants without OSA, there may be cardiac rhythm problems that are age related and are independent of peripheral endothelial dysfunction. We know that, with age, abnormal ECG rhythms and ventricular fibrillation are possible,[82] and increased BP has been indicative of vascular stiffness, which increases with age.[83] The OSA sample here showed higher BPV, higher brachial cuff BP readings, and QRS prolongation without associations with age. Separating by sex, we observed differences, specifically in females, with older participants with OSA than in the control group, and a corresponding greater number of menopausal women. These age and menopausal status differences may have contributed to some of the differences we observed, given links of autonomic function with hormonal status in some, although not all, studies.[84,85]

Unexpectedly, we found that the BP reading at the brachial cuff was significantly higher than the 5-minute average of CNAP-measured MBP. Since the CNAP device calibrates to a separate cuff BP measure,[61,86] this difference is unlikely to have been an artifact. A higher cuff BP most likely reflects white-coat hypertension.[30,87] This white-coat hypertension appeared to have been present only when a research team member took a manual reading, as opposed to when the researcher was standing close to the participant while the automated process was performed for the CNAP calibration (**Figure 1**, "CNAP initialization"). Another possible source of difference is that the brachial cuff measure was taken earlier in the visit while seated at a desk, whereas the CNAP measures were made after more than 10 minutes being seated with back support (**Figure 1**).

One potential limitation we could not explore is the validity of CNAP in people with compromised cardiovascular function.[88] Nevertheless, the ability to obtain continuous BP noninvasively allows for measures otherwise unobtainable. The separation by sex is not powered to draw generalizable conclusions, but we believe it is important to show the findings for females and males given the sex differences with respect to OSA and autonomic regulation.[53,54,89-91] Finally, the sleep parameters are not a reflection of the prior night's sleep, and instead may best reflect the presence or absence of OSA.

For future studies, we emphasize ensuring a consistent stabilization period prior to beginning CNAP recording.[92] We also recommend measuring state anxiety, which is strongly related to white-coat hypertension.[93] Similarly, we suggest asking participants about their level of relaxation or stress during the 5-minute "resting" period, as mental state could influence the cardiac measures. For the cuff BP measures, using the average of repeated measurements would align with American Heart Association guidelines.[92] Finally, larger sample sizes would help identify patterns that are not altered by inclusion or removal of outliers.

In conclusion, we observed higher BPV in participants with OSA, and more so in females. We also noted moderate correlations with only some cardiac variables, showing that BPV reflects physiology that is distinct from traditional metrics. We observed in males with OSA a prolonged QRS interval, which has been associated with later stages of cardiovascular pathophysiology. It remains difficult to distinguish OSA-specific patterns given the presence of cardiovascular risk factors in the sleep disorder, and the findings need expanding before they can be generalized to the larger population with OSA. Nevertheless, our findings show that observing dynamic processes with repeated measures, such as CNAP, can capture aspects of autonomic function not evident in standard clinical assessments. The clinical relevance of BPV requires evaluation with longitudinal CPAP studies that assess OSA status, cardiovascular health, and autonomic metrics.

ABBREVIATIONS

BP, blood pressure
BPV, mean arterial blood pressure variability
CNAP, continuous noninvasive arterial pressure
CPAP, continuous positive airway pressure
CVD, cardiovascular disease
DBP, diastolic blood pressure
ECG, electrocardiogram
HR, heart rate
HRV, heart rate variability
MBP, mean arterial blood pressure
OSA, obstructive sleep apnea
RR-I, RR interval
SBP, systolic blood pressure
TTPK, time to peak
UCLA, University of California, Los Angeles

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