RESEARCH ARTICLE

Inspiratory muscle strength training lowers blood pressure and sympathetic activity in older adults with OSA: a randomized controlled pilot trial

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Ramos-Barrera GE, DeLucia CM, Bailey EF. Inspiratory muscle strength training lowers blood pressure and sympathetic activity in older adults with OSA: a randomized controlled pilot trial. J Appl Physiol 129: 449–458, 2020. First published July 30, 2020; doi:10.1152/japplphysiol.00024.2020.—Previous work has shown lowered casual blood pressure after just 6 wk of inspiratory muscle strength training (IMST), suggesting IMST as a potential therapeutic in the prevention/treatment of hypertension. In this study, we assessed the effects of IMST on cardiovascular parameters in older, overweight adults diagnosed with moderate and severe obstructive sleep apnea (OSA). Subjects were randomly assigned to one of two interventions (1) high-intensity IMST ($n = 15$, 75% maximal inspiratory pressure), or 2) a control intervention ($n = 10$, 15% maximum inspiratory pressure). Subjects in both groups trained at home completing 30 training breaths/day, 5 days/wk for 6 wk. Pre- and posttraining measures included maximal inspiratory pressure, casual and ambulatory blood pressures, spontaneous cardiac baroreflex sensitivity, and muscle sympathetic nerve activity. Men and women in the high-intensity IMST group exhibited reductions in casual systolic (SBP), diastolic (DBP), and mean arterial blood pressures (MAP) [SBP: $-8.82 \pm 4.98$ mmHg; DBP: $-4.69 \pm 2.81$ mmHg; and MAP: $-6.06 \pm 1.03$ mmHg, $P < 0.002$] and nighttime SBP (pre: $-12.00 \pm 8.20$ mmHg; $P < 0.01$). Muscle sympathetic nerve activities were also lower ($-6.97 \pm 2.29$ bursts/min$^{-1}$; $P = 0.01$ and $-9.55 \pm 2.42$ bursts/100 heartbeats; $P = 0.002$) by week 6. Conversely, subjects allocated to the control group showed no change in casual blood pressure or muscle sympathetic nerve activity and a trend toward higher overnight blood pressures. A short course of high-intensity IMST may offer significant respiratory and cardiovascular benefits for older, overweight adults with OSA. For Clinical Trial Registration, see https://www.clinicaltrials.gov (Identifier: NCT02709941).

NEW & NOTEWORTHY Older, obese adults with moderate-severe obstructive sleep apnea who perform 5 min/day high-intensity inspiratory muscle strength training (IMST) exhibit lowered casual and nighttime systolic blood pressure and sympathetic nervous outflow. In contrast, adults assigned to a control (low-intensity) intervention exhibit no change in casual blood pressure or muscle sympathetic nerve activity and a trend toward increased overnight blood pressure. Remarkably, adherence to IMST even among sleep-deprived and exercise-intolerant adults is high (96%).

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repeated airflow obstruction (apnea) and airflow limitation (hypopnea) that result in sleep disruption and chronic intermittent hypoxemia (CIH). CIH has been linked to increases in reactive oxygen species and oxidative stress that contribute to sympathetic nervous system (SNS) hyperactivity (10, 35, 48, 65) and hypertension in an estimated 30–70% of OSA adults (1). The standard of care for OSA worldwide is continuous positive airway pressure (CPAP), which delivers a steady stream of pressurized air via a (nasal/oral) mask to stent the upper airway and stabilize breathing and blood oxygenation. Among adults with OSA and hypertension, nightly CPAP use improves spontaneous baroreflex sensitivity (BRS) (36, 67) and overall sympathetic nervous system activity (27, 39). However, these favorable outcomes are offset by uniformly low adherence, i.e., <4.4 h/night (18, 33, 38, 43), which continues to limit CPAP-related improvements in cardiovascular health (43).

Aerobic exercise is a first-line treatment for all stages of hypertension (74) and has well-documented benefits for blood pressure. Indeed, 2017 guidelines issued by the American Heart Association and American Cardiology Association advocate 150 min/week of aerobic exercise among the first-line treatments for all stages of hypertension (74) to lower blood pressure. Although traditional forms of aerobic exercise may improve BRS and lower blood pressure in OSA, the salient features of OSA including obesity [body mass index (BMI) >30] (19, 61, 75), lethargy (62, 66), and/or exercise intolerance (2, 6, 9, 26), often preclude sustained exertion (16, 41).

In recent years, a novel form of exercise known as inspiratory muscle strength training (IMST) has yielded surprising results including improvements in blood pressure and autonomic balance in patients with hypertension (23, 39) or OSA (70) and reductions in systemic vascular resistance in healthy young adults (17, 69). These outcomes are of interest and importance because in each case they were attained within 6 wk and with a training requirement of just 5 min/day for 5 days/wk or 25 min/wk total training time (70).

Whereas there is evidence that IMST performed daily lowers casual (resting) blood pressure and plasma catecholamines in adults with OSA and elevated or stage 1 hypertension (70), it is unclear what effect it may have on 24-h blood pressure, a better predictor of blood pressure related end-organ damage (25, 44). Accordingly, in the current study we obtained measurements of casual and continuous, noninvasive ambulatory blood pressure monitoring in a cohort of older (60–80 yr), predominately obese (i.e., BMI >30) adults with moderate-severe OSA [apnea hypopnea index (AHI) ≥15] pre-post 6-wk IMST. Because OSA is a recognized cause of secondary hypertension and sympathetic nervous system activity plays a fundamental role in raising blood pressure in this population (11), we also performed microneurography to quantitate sympathetic neural

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activity directed to vascular smooth muscle [i.e., muscle sympathetic nerve activity (MSNA)]. Last, whereas in a previous IMST study CPAP users had been excluded, the current study permitted inclusion of participants identified as adherent to CPAP or mandibular advancement devices (>4 h nightly use).

METHODS

This prospective, randomized double-blind controlled pilot clinical trial was conducted on adults with OSA who were recruited from the general population via advertisements placed in regional publications. Details about how the trial was conducted, reporting enrollment, allocation, follow-up, and analysis of subjects involved in the clinical trial are presented in a Consolidated Standards of Reporting Trials (CONSORT) flow chart (see Fig. 1) (21, 58). Exclusion criteria included asthma, history of respiratory disease, neurological impairment, head/neck or thoracic surgery, hypothyroidism, immune or nervous system impairments, recent history of infection, body mass index (BMI) >40 kg/m², apnea hypopnea index ≤15.0 events/hour sleep, majority mixed sleep apnea (i.e., obstructive and central apneas), majority central sleep apnea, anticoagulant medication, chronic heart failure, unstable angina, myocardial infarction, smoking, hypnotic or immunosuppressive medication, or cognitive disorders. Exclusion criteria for systolic blood pressure (SBP) was ≥150 and for diastolic blood pressure (DBP) ≥100. The upper limit for SBP is based on previous observations in OSA adults that show a propensity for slight increases in BP in some subjects during the first training week. In view of this possibility, we adopted a somewhat conservative cutoff for purposes of the pilot trial.

In accordance with the training device manufacturer guidelines (http://www.powerbreathe-usa.com/), subjects with presence/history of dyspnea, ruptured eardrum or other middle ear condition, history of rib fracture, and marked elevated left ventricular end-diastolic volume and/or pressure also were excluded from participation. Note that

![Consolidated Standards of Reporting Trials (CONSORT) flow chart. AHI, apnea hypopnea index; HSAT, home sleep apnea testing; IMST, inspiratory muscle strength training; AMBP, ambulatory blood pressure monitoring; BP, blood pressure; BRS, baroreflex sensitivity; PImax, maximal inspiratory pressure.](image-url)
individuals who were regular users of continuous positive airway pressure (CPAP) (or a related pressure therapy) or users of mandibular advancement dental devices were eligible to participate, as were subjects with elevated, stage 1, or stage 2 hypertension. The University of Arizona’s Human Subjects Protection Program approved the study procedures, and all subjects provided written informed consent before being enrolled. Some 200 adults responded to advertisements placed in a local newsletter, 136/200 adults completed the online screening questionnaire and were deemed eligible to complete the preassessments outlined below.

Assessments of lung function comprising assessments of forced expiratory volume in 1.0 s (FEV$_{1.0}$), forced vital capacity (FVC), forced inspiratory volume in 1.0 s (FIV$_{1.0}$), forced inspiratory capacity (FICV), FEV$_{1.0}$/FVC, FIV$_{1.0}$/FVC, FIV$_{1.0}$/FICV, peak expiratory flow (PEF), and peak inspiratory flow (PIF) (WinspiroPRO, Medical International Research, New Berlin, WI) in accordance with the guidelines of the American Thoracic Society (45). To determine maximal inspiratory pressure (PI$_{max}$), subjects generated a maximal inspiration from residual lung volume using the POWERbreathe training device in TEST mode. The average of the three trials defined the individual’s PI$_{max}$ (8, 31).

Home Sleep Apnea Testing

We used home sleep apnea testing (HSAT) to reliably identify those adults in our sample with moderate and severe OSA (50–52). The type 3 portable testing device (ApneaLink, ResMed, Bella Vista, Sydney, Australia) is validated for use in adults with moderate and severe OSA (20, 24, 46, 56) and captures blood oxygenation, nasal airflow, and thoraco-abdominal movement and yields estimates of the severity of sleep-disordered breathing based on monitoring time. These results are referred to as the respiratory event index (REI). Home sleep apnea testing also permitted exclusion of other forms of sleep disordered breathing (e.g., obesity hypoventilation syndrome or Cheyne Stokes Respiration) on the basis of nasal airflow disturbance, awake resting, and overnight oximetry measurement. Sleep quality, sleep duration, sleep efficacy, sleep latency, sleep disturbance, and impact on daily function using the Pittsburgh Sleep Quality Index (PSQI) (53) also were recorded.

Ambulatory Blood Pressure Monitoring

Eligible adults, who passed lung function assessments and had an AHI ≥15, completed a period of 24-h ambulatory BP monitoring (SOMNOTmedics, Randersacker, Germany). Given the propensity for sleep disturbance and arousal reactions to contribute to perturbations in SBP, we obtained continuous measures of SBP and DBP using a Food and Drug Administration-approved and European Society of Hypertension-validated SOMNOTouch noninvasive ambulatory blood pressure monitor (7). The device includes a small control unit worn on the wrist to measure pulse transit time (PTT), three-channel electrocardiogram (ECG) leads placed on the chest, and an oxygen monitor fitted to the finger that obviates the need for arm cuff inflations that may interfere with sleep quality (4).

After fitting each subject, the device was calibrated via a manual blood pressure measurement. Subjects were asked to refrain from any strenuous physical activity while wearing the device and to report back to the laboratory 24 h later for data download. For ambulatory recordings exceeding 4.0-h continuous recording overnight, beat-to-beat measures of blood pressure (BP) were averaged over the entire recording period and compared for consistency with repeated measures over shorter, i.e., 10 min, representative intervals (42).

In-Laboratory Procedures

Subjects initially underwent an in-laboratory blood draw and on a separate day underwent in-laboratory assessments of resting blood pressure, resting muscle sympathetic nerve activity (MSNA), and cardiorespiratory measures (see details below). Subjects were asked to refrain from caffeine and alcohol for 12 h and instructed not to eat for at least 4 h before their visit. Each of the measures was repeated at the 6-wk time point after completion of training.

Plasma catecholamines. Subjects underwent a fasting blood draw and were instructed to refrain from eating or drinking (anything other than water) and from taking over-the-counter pain or allergy medications for the 12 h leading up to the draw. Venous blood samples were collected between the hours of 0700 and 1000 from the antecubital region following 30 min of supine rest in a quiet, temperature-controlled room. Samples were placed on ice in lithium-heparin-coated tubes (BD Vacutainer, Franklin Lakes, NJ) and immediately centrifuged (4°C, 1,500 rpm, 15 min), and the plasma frozen was at −80°C. Plasma samples were analyzed via quantitative high-performance liquid chromatography (Associated Regional and University Pathologists–ARUP Laboratories, Salt Lake City, UT).

Resting blood pressure. In-laboratory measures of resting (seated) blood pressure were obtained at intake and study close and once weekly throughout the 6-wk intervention. Measures were taken in accordance with American Heart Association guidelines (55) with an automated oscillometric sphygmomanometer (SunTech CT40, SunTech Medical). Three measures, taken on alternate arms, were averaged to obtain systolic (SBP) and diastolic (DBP) blood pressures and to determine mean arterial pressure (MAP) using the equation: (MAP = DBP + 1/3(SBP – DBP)). Measures were obtained at the same time of day and on the same day each week for 6 wk.

Resting spontaneous cardiac baroreflex sensitivity. While subjects were semirecumbent and after a 20-min rest, we recorded lead II-EKG continuously (0.3–1.0 kHz) via Ag-AgCl surface electrodes placed on the chest (2.0 kHz) and beat-to-beat changes in systolic and diastolic blood pressures (SBP and DBP) at 1-min intervals via automated finger cuff pressure transducer (400 Hz) (ccNeXin; Bneye, Amsterdam, The Netherlands). Data were recorded online using a PowerLab (ADInstruments, Colorado Springs, CO) interface and LabChart 8 software. Moment-to-moment changes in the R-R interval (RRi) coincident with fluctuations in SBP were used to obtain estimates of cardiac baroreflex sensitivity (28, 29, 54) using proprietary software to identify “up” and “down” sequences (Cardioseries V2.4, Brazil). Sequences greater than 50 ms or cardiac oscillations that showed in beat-to-beat cycles that showed in beat-to-beat increases in SBP (≥1 mmHg) and lengthening of the R-R interval (≥6 ms) for each beat in the series or with beat-to-beat decreases in systolic blood pressure (≥1 mmHg), and shortening of the R-R interval (≥6 ms) for each beat in the series were included in this analysis (54, 63). Consecutive R-R intervals were plotted against SBP (mmHg) values in the preceding cycle to obtain regression lines and correlation values for each sequence. Correlation coefficients >0.85 were averaged to obtain individual subject estimates of spontaneous cardiac baroreflex sensitivity (ms/mmHg) (54). MSNA and beat-to-beat changes in (systolic and diastolic) blood pressure were recorded over 20 min of undisturbed rest. Data in the final 10 min of each recording were subject to analysis. Respiration-related motions of the chest wall (100 Hz) were recorded using respiratory belt transducers (ADInstruments, Colorado Springs, CO) placed around the chest and abdomen. All data were recorded continuously throughout ~20 min of undisturbed rest.
Table 1. Average values for age, body mass index, neck circumference, respiratory disturbance index, Pittsburgh Sleep Quality Index, obstructive sleep apnea therapy type, cardiovascular risk category, blood pressure medication/s, and level of physical activity reported by participants in the control group and high-intensity IMST group at study intake

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Intervention Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n = 10)</td>
</tr>
<tr>
<td>Subjects</td>
<td>6 men, 4 women</td>
</tr>
<tr>
<td>Age</td>
<td>69.7 ± 6.7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>31.3 ± 6.5</td>
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<tr>
<td>Neck circumference, cm</td>
<td>41.0 ± 3.9</td>
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<tr>
<td>RDI</td>
<td>26.2 ± 13.5</td>
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<tr>
<td>PSQI</td>
<td>9.0 ± 5.0</td>
</tr>
<tr>
<td>OSA therapies</td>
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</tr>
<tr>
<td>Continuous positive airway pressure</td>
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<tr>
<td>Mandibular advancement device</td>
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</tr>
<tr>
<td>No device</td>
<td>6</td>
</tr>
<tr>
<td>Cardiovascular risk category</td>
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</tr>
<tr>
<td>Normal (systolic) BP (&lt;120 mmHg)</td>
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</tr>
<tr>
<td>Elevated systolic BP (120–129 mmHg)</td>
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</tr>
<tr>
<td>Stage 1 hypertension (130–139 mmHg)</td>
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</tr>
<tr>
<td>Stage 2 hypertension (≥140 mmHg)</td>
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<tr>
<td>BP medications</td>
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</tr>
<tr>
<td>Beta-blocker</td>
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</tr>
<tr>
<td>Angiotensin receptor blocker</td>
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</tr>
<tr>
<td>Calcium channel blocker</td>
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</tr>
<tr>
<td>ACE inhibitor</td>
<td>3</td>
</tr>
<tr>
<td>No BP medication</td>
<td>5</td>
</tr>
<tr>
<td>Physical activity levels</td>
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<td>Minimally active (0–2 h exercise/wk)</td>
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</tr>
<tr>
<td>Moderately active (3–4 h exercise/wk)</td>
<td>4</td>
</tr>
<tr>
<td>Vigorously active (&gt;5 h exercise/wk)</td>
<td>4</td>
</tr>
</tbody>
</table>

Average values ± SD for age, body mass index (BMI), neck circumference, respiratory disturbance index (RDI), Pittsburgh Sleep Quality Index (PSQI), obstructive sleep apnea (OSA) therapy type, cardiovascular risk category, blood pressure (BP) medication/s and level of physical activity reported by participants in the control group (n = 10) and high-intensity inspiratory muscle strength training (IMST) group (n = 15) at study intake. BMI, body mass index; ACE, angiotensin-converting enzyme.

Amp Ex; ADInstruments, Colorado Springs, CO) and signals were full wave rectified (0.1-s moving window) and stored (10-kHz sampling) using a computer-based data acquisition and analysis system (LabChart 8.0 software, ADInstruments, Colorado Springs, CO). Electrode position in muscle fascicles was confirmed by pulse synchronous bursts of activity, elicitation of afferent nerve activity by mild muscle stretch and absence of response to startle (40).

Negative deflecting cardiac-related sympathetic action potentials were identified using both unprocessed and root mean squared MSNA signals and quantitated as the number of bursts per 100 heartbeats, number of bursts per minute, and total activity (mean burst area/min) obtained from the root mean square (RMS) processed (moving average time constant or 200 ms) signal (47, 49, 60, 68, 71, 72). The recording period was started no earlier than 15 min after insertion of the electrode and was continuous throughout ~20 min of undisturbed rest.

6-wk Intervention

Twenty-five adults (17 men, 8 women) were prospectively assigned, via stratified block randomization to high-intensity IMST (n = 15) or to the control condition (n = 10), outlined below. All subjects were unfamiliar with IMST, and all were blinded to their assigned training group.

Subjects in both groups trained independently at home completing 30 breaths, i.e., 5 sets of 6 breaths with a ~1- to 2-min rest between each set, 5 days/wk for 6 wk on the POWERbreathe device (K3 Series, Warwickshire, UK). Training was performed at the same time each day, and data from each day’s training were stored on the device and uploaded in the laboratory at the end of each training week. Subjects were instructed first to exhale to residual volume and then inhaled via the device mouthpiece to their target pressure. As previously, target pressures for the control group were set to 15% of the PImax, and those for the high-intensity IMST group were set to 75% of the PImax (17, 69, 70). Neither group encountered resistance to expiration. Because IMST improves inspiratory muscle strength and subjects in both groups typically show improvement in PImax test performance, target pressures for both groups (i.e., 15% or 75% PImax) were reassessed at the end of each training week.

Statistical Analysis

A per protocol, two-way repeated-measures mixed model ANOVA was used to test the main effects of treatment (IMST vs. control) and time point (week 1 vs. week 6). Statistical significance was set at P ≤ 0.05. If the ANOVA revealed significance, planned post hoc within-group and between-group comparisons were performed using paired
and cardiac baroreflex sensitivity for subjects in the high-intensity IMST group, pre- and postintervention

### Table 2. Average values for respiratory disturbance index; systolic, diastolic; and mean arterial pressure, heart rate; and cardiac baroreflex sensitivity for subjects in the high-intensity IMST group, pre- and postintervention

<table>
<thead>
<tr>
<th>Cardiovascular measures</th>
<th>High-Intensity IMST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>140.8 ± 17.9</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>74.9 ± 9.9</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>95.0 ± 11.2</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>59.2 ± 5.4</td>
</tr>
<tr>
<td>BRS, ms/mmHg</td>
<td>10.4 ± 3.9</td>
</tr>
<tr>
<td>Plasma norepinephrine, 80–520 pg/mL</td>
<td>307.1 ± 69.1</td>
</tr>
<tr>
<td>Plasma epinephrine, 10–200 pg/mL</td>
<td>28.0 ± 13.8</td>
</tr>
</tbody>
</table>

Average values ± SD for respiratory disturbance index (RDI); systolic, diastolic, and mean arterial blood pressures; heart rate; and cardiac baroreflex sensitivity (BRS) for subjects in the high-intensity inspiratory muscle strength training (IMST) group (n = 14), pre (week 1)- and postintervention (week 6).

*Significant difference pre vs. post (P < 0.01).

#### RESULTS

Twenty-five adults were randomized to high-intensity IMST or the control intervention. One subject was disqualified from continuing the study due to nonadherence to the training regimen. As a result, the study retention rate was 96%. There were no between-group differences in sex, age, neck circumference, BMI, systolic and diastolic BP, respiratory disturbance index, or PSQI scores (P > 0.1) at study intake. Details of subject number, anthropomorphic data, and health status (i.e., sleep apnea severity, sleep apnea therapy, cardiovascular risk category, medications and physical activity levels) for high-intensity IMST and control groups are presented in Table 1.

Overall, key sleep indexes including awake and resting oxygen desaturations, and sleep duration, were unchanged pre- and postintervention for both groups (P > 0.1). Maximum inspiratory pressures (PImax) were greater pre-post for IMST (82.6 ± 12.5 to 116.5 ± 13.6 cmH2O) (P < 0.001) and control groups (85.60 ± 4.5 to 101.2 ± 6.94 cmH2O) (P < 0.01), but there was no effect of either intervention on tests of pulmonary function: FEV1.0; FVC; FIV1.0/FVC; FIV1.0/FIVC; PEF; or PIF (P > 0.05) (data not shown).

Individual results for casual in-laboratory measures of systolic, diastolic, and mean arterial blood pressures are shown in Fig. 2. For the high-intensity IMST group, average (±SD) SBP, DBP, and MAP all declined from week 1 to week 6 (SBP: −8.82 ± 4.98; DBP: −4.69 ± 2.81; and MAP: −6.06 ± 1.03; P < 0.002). Heart rate and BRS were unchanged (Table 2). For the control group, measures of blood pressure (SBP: −2.23 ± 6.85; DBP: −1.16 ± 14.20; MAP: −4.08 ± 13.06) and sleep apnea severity (RDI, −2.28 ± 14.2) remained unchanged (P > 0.05).
DBP: $-1.10 \pm 3.96$; and MAP: $-1.48 \pm 4.60$), heart rate ($2.2 \pm 2.4$ beats/min), and BRS ($-0.31 \pm 1.9$ ms/mmHg) were unchanged pre vs. post ($P > 0.1$).

Ambulatory blood pressure and MSNA recordings were obtained in a subset of individuals, pre- and postintervention (9 high-intensity and 6 control). Group data for high-intensity IMST are provided in Table 3 and results for individuals in both groups are shown in Fig. 3. Despite overall declines in nighttime BP, only results for SBP (pre: $141.56 \pm 18.93$ mmHg; post: $129.55 \pm 15.67$ mmHg) attained significance ($P < 0.01$). Nighttime DBP (pre: $76.56 \pm 8.88$ mmHg; post: $74.11 \pm 9.22$ mmHg) and MAP (pre: $98.67 \pm 11.19$; post: $92.78 \pm 8.73$ mmHg) (Fig. 3) also

![Fig. 4](representative recordings (30 s) of muscle sympathetic nerve activity (MSNA), blood pressure (BP), electrocardiogram (EKG), and chest wall motion traces from 4 obstructive sleep apnea (OSA) adults pre (week 1) and post (week 6) high-intensity inspiratory muscle strength training (IMST). RMS, root mean squares. *Sympathetic bursts included in participant's average burst/min count.}

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declined but did not attain statistical significance \((P < 0.10)\). In the control group, average \((\pm SD)\) nighttime SBP (pre: 135.14 \(\pm\) 13.13; post: 144.67 \(\pm\) 19.10 mmHg), DBP (pre: 73.17 \(\pm\) 13.63; post: 77.17 \(\pm\) 13.72 mmHg) and MAP (pre: 93.83 \(\pm\) 13.67; post: 100.33 \(\pm\) 15.67 mmHg) slightly increased postintervention \((P > 0.05)\) (Fig. 3).

Results for in-laboratory measures of resting MSNA for high-intensity IMST are provided in Table 3 and representative recordings in Fig. 4. Average measures of MSNA bursts per minute \((-6.97 \pm 2.29; \ P = 0.01)\) and bursts per 100 heartbeats \((-9.55 \pm 2.42; \ P = 0.002)\) were lower at week 6 than in week 1 following high-intensity IMST but did not change following the control intervention \((4.87 \pm 2.80 \text{bursts/min}^{-1}; \ P = 0.10)\) and \(5.52 \pm 2.96 \text{bursts/100 heartbeats}; \ P = 0.85)\) (Fig. 5). Neither training protocol was associated with significant changes in plasma norepinephrine \((\text{high-intensity IMST: pretraining 307.10}\ \mu\text{g/L; post: 197.40}\ \mu\text{g/L}; \ P = 0.05)\) (Fig. 3). 

**DISCUSSION**

OSA is characterized by repeated airway obstructions that result in intermittent hypoxemia and arousal from sleep, which together drive increases in nighttime sympathetic nervous activity (64). Although previous studies confirm the benefits of CPAP and/or daily exercise on cardiovascular health (3, 5, 22, 36, 67), adherence rates for CPAP remain low (43). Furthermore, many adults with OSA are unwilling or unable to maintain a regular exercise program (2, 6).

Compared with traditional forms of aerobic exercise, retention rates for IMST are consistently high (92–95%) exceeding those of comparable duration lifestyle, i.e., aerobic exercise and/or dietary interventions (30, 37). With no treatment-emergent adverse events and a 96% adherence rate \(\left(\text{number of prescribed training sessions completed at the target pressure}\right)\), IMST appears well tolerated by the OSA population.

**Strengths and Limitations**

Participants were recruited via advertisements in a regional publication. The general recruitment call yielded two groups, well matched in regard to key parameters of sex, age, BMI, CPAP use, and sleep apnea severity \((\text{see Table } 1);\) however, we acknowledge that we were unable to obtain complete data sets from all our subject participants and that the requirement for pre- and post-24-h blood pressure monitoring and MSNA recordings posed a particular challenge in this population. While subject loss does not limit the generalizability of the lower probability outcomes \((i.e., \ P < 0.05)\), the variability inherent in smaller samples may contribute false negative outcomes, which may have affected outcomes for measures of overnight BP.

Sleep and nighttime breathing including blood oxygen desaturation (32), nasal airflow, and thoraco-abdominal movement were monitored using an in-home sleep apnea testing \((\text{HSAT})\) validated for use in adults with moderate and severe OSA (20, 46, 56). Importantly, the device assesses time spent with blood oxygen desaturation \(<90\%\), nasal airflow, and thoraco-abdominal movement and the intraclass correlation between results obtained with this form of home sleep apnea testing and with overnight PSG is excellent (12).

Pre- and post-HSAT showed no evidence of intervention-related changes in apnea frequency \((\text{respiratory disturbance index})\), oxygen desaturation \((<90\%)\), total sleep time, and modest improvements in subjects’ subjective assessment of sleep quality \((\text{PSQI})\). The latter outcome differs from previously published findings in adults with mild-moderate OSA (70) who reported improved sleep quality \((\text{PSQI})\) under the same IMST protocol. Nevertheless, because weight, neck circumference, physical activity, medications, sleep quality, and AHI each remained consistent throughout the study period, the observed reductions in casual and overnight SBP and SNS hyperactivity cannot be ascribed to change/s in the aforementioned variables.

Care was taken to exclude participants with prior knowledge of or experience with inspiratory muscle strength training. Whereas participants in both groups trained on the same handheld pressure-threshold training device, followed the same training regimen \((i.e., 30 \text{ breaths day for } 5 \text{ days/wk for } 6 \text{ wk});\) and attended weekly laboratory visits and reassessments, all visits were coordinated to preclude participant overlap to ensure participant blinding to high-intensity IMST versus control intervention formats.

As described previously, training pressures for the control group were significantly lower than for the high-intensity group \((i.e., 15\%\text{Pmax} \text{ vs. } 75\%\text{Pmax})\). However, the pressure range for the control group encompassed \(-15.0 \text{ to } -20.0 \text{ cmH2O}\) exceeding pressures typical of tidal (73) or deep breathing (34). We anticipated the control intervention may contribute some improvement in inspiratory muscle strength; however, the magnitude of the increase in \(\text{Pmax} \approx -5 \text{ cmH2O})\) is consistent with previously published findings in healthy adults.
(17) and consistent with “learning”-related improvements attributable to repeat testing over a short time span (57, 59).

**Mechanistic Insights into Improvement in Blood Pressure**

The mechanisms responsible for the favorable effects of IMST require further elucidation. As reported previously in healthy adults, large (positive or negative) intrathoracic pressure swings do not alter lung volume excursions appear to be the primary (respiratory) stimulus underpinning IMST-related reductions in BP (69). However, we see no evidence of IMST-related changes in baroreflex sensitivity, heart rate, or cardiac output (17). Although cardiac output was not among the primary or secondary end points of the current study, estimates of cardiac output (CO) retrieved from in-laboratory continuous monitoring of BP (ccNexfin, Bmeye, Amsterdam, The Netherlands) indicate no changes in CO for either the high-intensity (2.67 ± 5.53% change) or control group (3.41 ± 6.39% change) relative to preintervention values. However, as these estimates of cardiac output were derived from discontinuous data obtained pre- and postintervention, they must be interpreted with caution and are subject to reassessment using more traditional (e.g., equilibration CO2 rebreathing) approaches.

In contrast, there is evidence of IMST-related declines in plasma catecholamines (70), peripheral resistance (17), endothelial-dependent dilation (14) and sympathetic nervous outflow (current findings) that point to changes in vascular function (15). Specifically, a focus on peripheral artery stiffness appears warranted given preliminary evidence of IMST-related improvements in peripheral artery distensibility and increased nitric oxide bioavailability in otherwise healthy older healthy adults (15). Whether a similar vascular benefit might occur in the context of OSA will require further study.

**Summary**

Our results confirm previously reported findings of IMST-related improvements in casual blood pressure. In addition, the current findings provide preliminary and novel support for the potential for high-intensity IMST to reduce resting sympathetic neurogenic activity and nighttime systolic blood pressure among older, overweight adults with OSA with just 5 min training/day. Given these findings we propose that high-intensity IMST may be an effective intervention for lowering BP among older adults with OSA. Whether IMST can confer similar benefits when implemented in younger adults with OSA and hypertension and whether the benefits aggregate over the longer term (6–12 mo) and diminish upon withdrawal awaits further study.

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