Inspiratory Resistance, Cerebral Blood Flow Velocity, and Symptoms of Acute Hypotension

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Introduction: Symptoms of orthostatic intolerance, e.g., following prolonged bed rest and microgravity exposure, are associated with reductions in cerebral blood flow. We tested the hypothesis that spontaneously breathing through an impedance threshold device (ITD) would attenuate the fall in cerebral blood flow velocity (CBFV) during a hypotensive orthostatic challenge and reduce the severity of reported symptoms. ***Methods:*** While breathing through either an active ITD (−7 cm H_2O inspiratory impedance) or a sham ITD (no impedance), 19 subjects performed a squat stand test (SST). Symptoms upon stand were recorded on a 5-point scale (1 = normal; 5 = faint) of subject-perceived rating (SPR). To address our hypothesis, only data from symptomatic subjects (SPR > 1 during the sham trial) were analyzed ($N = 9$). Mean arterial blood pressure (MAP) and mean CBFV were measured continuously throughout the SST and analyzed in time and frequency domains. ***Results:*** Breathing with the active ITD during the SST reduced the severity of orthostatic symptoms in eight of the nine symptomatic subjects (sham ITD SPR, 1.9 ± 0.1; active ITD SPR, 1.1 ± 0.1), but there was no statistically distinguishable difference in the reduction of mean CBFV between the two trials (sham ITD, −39 ± 3% vs. active ITD, −44 ± 3%). High frequency oscillations in mean CBFV, however, were greater during the active ITD trial ($7.8 \pm 2.6\ cm \cdot s^{-2}$) compared with the sham ITD trial ($2.5 \pm 0.9\ cm \cdot s^{-2}$). ***Conclusions:*** Higher oscillations in CBFV while breathing with the active ITD may account for the reduction in symptom severity during orthostatic hypotension despite the same fall in absolute CBFV.

Keywords: impedance threshold device, hemodynamic oscillations, cerebral blood flow regulation, squat-stand test, hypotension.

THE INABILITY TO maintain adequate cerebral blood flow can lead to clinical presyncopal symptoms or unconsciousness during hemodynamic challenges such as hemorrhage, cardiac arrest, and orthostasis (e.g., following prolonged bed rest or microgravity exposure) (14,21). An impedance threshold device (ITD) was designed to create a greater intrathoracic vacuum during the inspiratory phase of the breathing cycle and subsequently increase venous return and ventricular preload (12,16,17). This vacuum elevates cardiac output ($\dot{Q}$) and arterial blood pressure in patients following cardiac arrest (22), in experimental models of severe central hypovolemia in humans (7), and in animal models of severe hemorrhage (17). The ITD also reduces intracranial pressure and increases cerebral perfusion following hemorrhage in animals (30,31) and increases oscillations in cerebral blood flow velocity (CBFV) in humans with experimentally induced central hypovolemia (25).

Spontaneously breathing through an ITD ameliorates the reduction in arterial blood pressure with central hypovolemia in healthy, normotensive subjects (5,25) and individuals with clinical orthostatic hypotension (18). Subjects also reported a reduction in symptoms of orthostatic stress (e.g., dizziness, nausea, and lightheadedness) with the ITD in all of these studies (5,18,25). We speculated that less severe symptoms reflect a capability for the ITD to protect cerebral perfusion during an orthostatic challenge (5). Using the squat-stand test (SST) as the stimulus for acute, transient reductions in arterial blood pressure (8,24) and CBFV (23), we tested the hypothesis that breathing through the ITD would attenuate the reduction in CBFV and reduce the severity of presyncopal symptoms.

METHODS

Subjects

There were 19 (7 female, 12 male) healthy, normotensive, nonsmoking subjects (age 34 ± 2 yr; height 170 ± 3 cm; weight 76 ± 4 kg) who volunteered to participate in this study conducted at the Kennedy Space Center, FL. All experimental procedures and protocols were reviewed and approved by the Institutional Review Board of the Kennedy Space Center. A complete medical history

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and physical examination that included a clinical orthostatic exam (consecutive supine/seated/standing blood pressure measurements) was obtained on each of the potential subjects prior to being approved for testing. Subjects were instructed to refrain from exercise, alcohol, and stimulants such as caffeine and other nonprescription drugs for 24 h prior to testing in order to reduce any potential acute effects on cardiovascular responsiveness and orthostatic tolerance. Each subject attended a one-on-one briefing session, read a detailed information sheet, and gave their written informed consent prior to participating in the study.

Instrumentation and Data Acquisition

Continuous heart rate was measured from a standard electrocardiogram (ECG). Real-time, beat-to-beat, continuous estimates of arterial blood pressure were measured noninvasively using infrared finger plethysmography with a Portapres™ blood pressure monitor (TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands). An appropriately sized Portapres™ blood pressure cuff was placed on the middle finger of the left hand, which was held to the chest at heart level using an arm sling. Resting, seated blood pressure measurements were verified against a previously collected manual sphygmomanometer recording to validate Portapres™ readings [no difference for systolic (SBP) or diastolic blood pressure (DBP), $P \geq 0.13$].

CBFV of the left middle cerebral artery (MCA) was recorded using a 2-MHz Doppler probe (EZ-Dop®, DWL Elektronische Systeme GmbH, Sipplingen, Germany) positioned at a constant angle over the temporal window, located above the zygomatic arch (20). The transcranial Doppler procedure for measuring CBFV has previously been described in detail (1,20). Briefly, the ultrasound signal emitted from the Doppler probe is reflected from erythrocytes within the MCA and back to the probe. The difference in frequency between the emitted signal and the reflected signal, the Doppler shift, is used to calculate MCA blood flow velocity via fast Fourier transform analysis (20). The resultant waveform (similar to a blood pressure waveform) is produced via spectral analysis of the blood flow velocity signal (21). Inspiratory and expiratory pressures were recorded using a commercial pressure transducer (All Sensors Corporation, Morgan Hill, CA) connected to the collar between the mouthpiece and ITD via a small piece of flexible rubber tubing.

Protocol

Each subject participated in two experimental trials, consisting of a SST: 1) while spontaneously breathing through a mouthpiece connected to an active ITD (Advanced Circulatory Systems Inc., Eden Prairie, MN) set at a resistance of approximately −7 cm H_2O; and 2) during a control session where subjects spontaneously breathed through a mouthpiece connected to a sham ITD (0 cm H_2O), designed with the identical appearance to the active ITD, but without significant inspiratory resistance.

The SST protocol consisted of a 4-min seated baseline period (T = 0:00–4:00 min) followed by a 4-min squat (T = 4:00–8:00 min), where subjects were instructed to assume a squatting position as deeply as possible while maintaining balance without touching the floor with their hands. At T = 7:45 min of the protocol (15 s prior to the transition to the stand posture), subjects were given either the active or sham ITD attached to a mouthpiece and were instructed to commence breathing through the device. To ensure subjects breathed entirely through their mouths, a clip was placed firmly over the nose during both the active and sham ITD interventions, optimizing the inspired negative pressure transfer to the intrathoracic cavity. At T = 8:00 min, subjects were instructed to stand erect from the squatting position as quickly as possible without using their hands to assist them, then remain in the standing position for a further 4 min. Subjects continued to breathe through the active or sham ITD during the squat-to-stand transition and throughout the stand phase. At the conclusion of the 4-min stand phase (T = 12:00 min), subjects returned to the seated position where they remained for a minimum of 30 min prior to commencing the second trial. Each experimental session was conducted within 90 min.

Within approximately 10 s of standing, subjects were requested to nonverbally indicate their orthostatic symptoms based on a 5-point scale (1 = normal, 2 = mild, 3 = moderate, 4 = severe, and 5 = faint) of subject-perceived rating (SPR). Once subjects were seated at the conclusion of the stand phase, they completed a comprehensive survey to identify which of the following symptoms they experienced upon standing: lightheadedness, headache, fatigue, visual disturbances, weakness, difficulty breathing, trembling, sweating, palpitations, and nausea. There were nine subjects (two female, seven male) who reported at least one orthostatic symptom upon transition to the standing posture during the sham ITD trial (age, 34 ± 3 yr; height 169 ± 4 cm; weight 79 ± 6 kg). The results are derived from these nine subjects only, as we were interested in the effect of active ITD breathing on attenuating symptoms during orthostasis and the association between symptoms and cerebral blood flow regulation. Of these nine subjects, three were tested with the sham ITD first and six were tested with the active ITD first.

Data Analysis

Continuous, beat-to-beat ECG, Portapres™, Doppler, and breath-to-breath ITD pressure recordings were interfaced with an analog-to-digital converter, then recorded directly to a computer-based data acquisition software package (WinDAQ, Dataq Instruments, Akron, OH) at a sampling frequency of 500 Hz. Following calibration, the data were imported into analysis software (WinCPRS, Absolute Aliens, Turku, Finland). R waves generated from the ECG signal were detected and marked at their occurrence in time. DBP and SBP and diastolic and systolic CBFVs were subsequently marked from the Portapres™ and Doppler tracings. Mean arterial pressure (MAP) and mean CBFV were automatically

calculated as the area under the arterial pressure waveform and CBFV waveform via the WinCPRS software.

All time and frequency domain variables were calculated from the final 3 min of the seated baseline period (T = 1:00–4:00) and 3 min of the squatting period prior to application of the active or sham ITD (T = 4:30–7:30 min). The nadirs of the MAP and CBFV responses were detected upon transition from the squat to stand posture under both ITD conditions. The percentage changes (%Δ) from squat to stand were subsequently calculated for these variables. For frequency domain variables, the first 3 min of data following stand (T = 8:00–11:00 min) were analyzed under both ITD conditions. The average number of beats used for each time frame of interest were: sham ITD: squat = 259 ± 21 points; stand = 260 ± 18 points; active ITD: squat = 268 ± 22 points; stand = 271 ± 18 points.

Oscillatory patterns of MAP and mean CBFV were determined with fast Fourier power spectral analysis. Data were made equidistant by interpolating linearly and resampling at 5 Hz. Data were then passed through a low-pass impulse response filter with a cutoff frequency of 0.5 Hz. To obtain power spectra, 3-min data sets were fast Fourier transformed with a Hanning window. Spectral power was expressed as the integrated area within the low-frequency (LF = 0.04–0.15 Hz) and high frequency (HF = 0.15–0.4 Hz) ranges, and total power was calculated as the sum of HF and LF, excluding oscillations occurring below 0.05 Hz (3,28). We present the data both in absolute and normalized units. The data were normalized in the HF (HF nu) and LF (LF nu) ranges by dividing the LF and HF spectra by the total power.

The coherence among MAP and mean CBFV was calculated by dividing the cross-spectral densities of the two signals by the product of the individual autospectra. Low coherence values (< 0.50) indicate effective cerebral autoregulation as the signals are independent of each other, while high coherence values indicate a linear association between CBFV and MAP, which may represent ineffective autoregulation (13,34). At the LF where signals are coherent (i.e., ≥ 0.5), transfer function magnitudes among MAP and mean CBFV represent a frequency dependence of dynamic cerebral autoregulation (33). The transfer function magnitude expressing the frequency relation of cerebral autoregulation was calculated by dividing the cross-spectrum of MAP and mean CBFV by the autospectrum of MAP. Transfer functions were considered valid and averaged at the LF only when coherence values were ≥ 0.5.

Two additional techniques were used to assess cerebral autoregulation within the acute stages of the SST (first 10-30 s) as previously reported by this laboratory (23). First, once the nadirs of both the MAP and CBFV responses were determined following the assumption of the standing posture, the time to nadir was calculated from the time of stand, and the time to recovery was calculated from the time of stand to the point where MAP and CBFV returned to baseline levels. Second, the relationship between the responses of MAP and CBFV was assessed via linear regression analysis. Regression analyses were performed on beat-to-beat MAP and CBFV responses for each subject over the time that MAP took to reach the nadir value following stand. Coefficients of determination (R^2) were calculated to provide an index of autoregulatory failure, while the slope of this relationship was used to indicate the severity of this failure when R^2 was greater than 0.75 (21).

Statistical Analysis

Two-way repeated measures ANOVAs were used for the comparison of all physiological variables in the symptomatic subjects, followed by Tukey post hoc tests. Paired student *t*-tests were used to compare percentage change values (%Δ) during the stand phase between the active ITD and sham ITD trials. All data are presented as mean ± SE and exact *P*-values are presented for all comparisons (10,15).

RESULTS

Breathing on the active ITD during the SST reduced the severity of orthostatic symptoms in eight of the nine symptomatic subjects (sham ITD SPR, 1.9 ± 0.1; active ITD SPR, 1.1 ± 0.1; $P = 0.001$). As shown in **Table I**, however, mean CBFV and MAP fell precipitously upon the transition from squat to stand under both the sham and active ITD conditions ($P < 0.001$), and between conditions (active vs. sham) the probability associated with these responses was ≥ 0.20 when represented as % change from squat (**Fig. 1**).

TABLE I. TIME DOMAIN RESPONSES DURING THE SHAM ITD AND ACTIVE ITD TRIALS.

Variable	Sham ITD			Active ITD			Sham vs. Active
	Squat	Stand	*P*-Value	Squat	Stand	*P*-Value	*P*-Value (Stand vs. Stand)
Mean CBFV, cm · s^{-1}	66 ± 5	39 ± 3	< 0.001	67 ± 6	37 ± 5	< 0.001	0.619
Systolic CBFV, cm · s^{-1}	98 ± 8	81 ± 8	0.002	101 ± 9	78 ± 9	< 0.001	0.646
Diastolic CBFV, cm · s^{-1}	45 ± 4	19 ± 3	< 0.001	44 ± 5	16 ± 4	< 0.001	0.241
MAP, mmHg	111 ± 2	65 ± 5	< 0.001	107 ± 2	57 ± 4	< 0.001	0.007
HR, bpm	87 ± 7	114 ± 6	< 0.001	90 ± 7	119 ± 6	< 0.001	0.081
Respiratory Rate, breaths/min *	-	11.9 ± 0.9	-	-	10.4 ± 0.7	-	0.012

Values are mean ± SE; *N* = 9 for all variables except for respiratory rate where *N* = 8 (*). ITD, inspiratory threshold device; CBFV, cerebral blood flow velocity; MAP, mean arterial pressure; HR, heart rate.

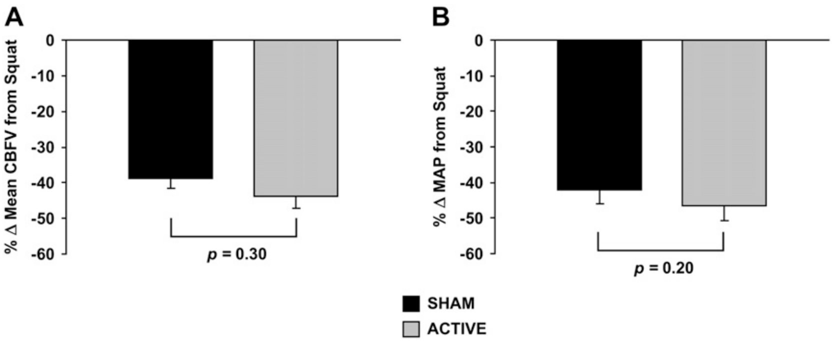

Fig. 1. The percentage change (% Δ) responses from squat to stand (nadir) for mean cerebral blood flow velocity (CBFV, panel A) and mean arterial pressure (MAP, panel B) for the nine symptomatic subjects during the sham (black bars) and active (gray bars) ITD trials. Data are means ± SE.

By comparison, analysis of the frequency domain for CBFV and MAP revealed significant effects of ITD breathing. As demonstrated in **Fig. 2**, spontaneously breathing through the active ITD during the stand phase of the SST increased total oscillations in CBFV and MAP compared with the sham ITD trial ($P \leq 0.061$). Data contained in **Table II** indicates the increase in HF oscillations with active ITD breathing accounts for this increase in total oscillations for CBFV, while both LF and HF oscillations increase for MAP. Similarly, HF oscillations were higher in both SBP (7.1 ± 1.6 vs. 16.7 ± 3.9 $mmHg^2 \cdot Hz^{-1}$, $P < 0.001$) and systolic CBFV [3.9 ± 1.0 vs. 10.2 ± 3.0 $(cm \cdot s^{-2}) \cdot Hz^{-1}$, $P = 0.007$], and in DBP (1.3 ± 0.5 vs. 4.4 ± 1.6 $mmHg^2 \cdot Hz^{-1}$, $P = 0.038$) and diastolic CBFV [2.2 ± 0.8 vs. 6.5 ± 1.9 $(cm \cdot s^{-2}) \cdot Hz^{-1}$, $P = 0.008$] during the active ITD trial. **Fig. 3** is a typical representative tracing of the mean CBFV responses during the first 3 min of stand during both the sham and active ITD trials in one subject. Note the increase in the amplitude and regularity of the oscillations during the active ITD trial, and the higher absolute velocities during the initial 30 s of stand when symptoms were reported (shaded area).

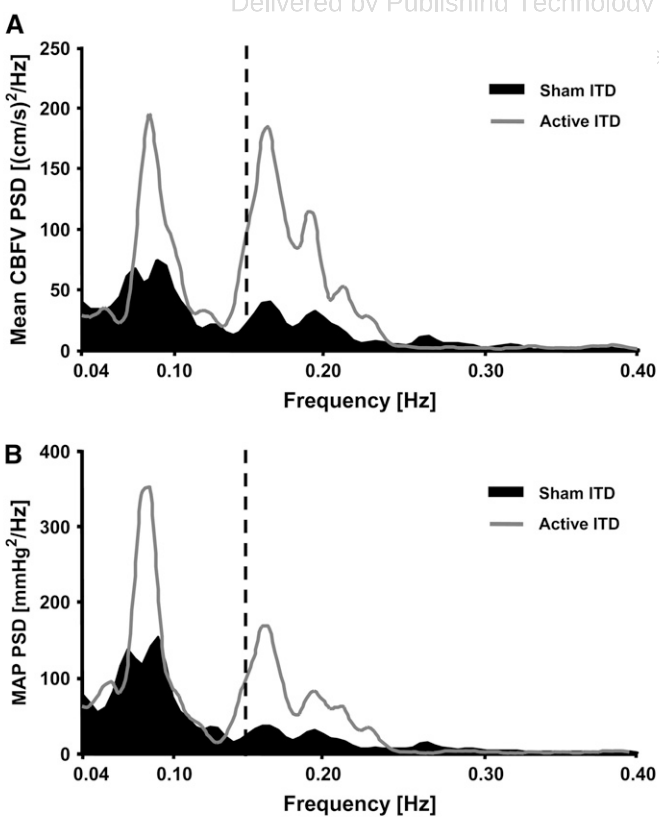

Fig. 2. Average mean cerebral blood flow velocity (CBFV, panel A) and mean arterial pressure (MAP, panel B) power spectral density (PSD) during the first 3 min of stand for the sham and active ITD trials. The vertical dashed line represents the separation of low frequency (LF, 0.04–0.15 Hz) and high frequency (HF, 0.15–0.4 Hz) spectral bands.

Coherence values between MAP and mean CBFV upon standing were similar between the two conditions (sham ITD, 0.67 ± 0.04 vs. active ITD, 0.74 ± 0.04, $P = 0.277$) (Table II). Likewise, analysis of the transfer function magnitudes among MAP and mean CBFV upon standing did not indicate a statistically distinguishable difference between sham [0.65 ± 0.08 $(cm \cdot s^{-1}) \cdot mmHg^{-1}$] and active [0.70 ± 0.08 $(cm \cdot s^{-1}) \cdot mmHg^{-1}$] ITD conditions ($P = 0.610$) (Table II). Time to nadir ($P \geq 0.208$) and time to recovery ($P \geq 0.585$) responses for MAP and CBFV under sham and active ITD conditions were similar (time to nadir: sham ITD, MAP 7.3 ± 0.6 s and CBFV 4.5 ± 0.4 s; active ITD, MAP 7.5 ± 0.6 s and CBFV 5.6 ± 1.0 s; time to recovery: sham ITD, MAP 21.5 ± 5.3 s and CBFV 14.6 ± 1.8 s; active ITD, MAP 21.8 ± 6.0 s and CBFV 12.9 ± 0.9 s). The average R^2 values were < 0.75 between the responses of MAP and CBFV upon standing for both the active ITD ($R^2 = 0.50 \pm 0.11$) and sham ITD ($R^2 = 0.68 \pm 0.10$) conditions ($P = 0.196$).

DISCUSSION

We hypothesized that spontaneously breathing through an active ITD during an orthostatic challenge would attenuate the decrease in CBFV and reduce the severity of presyncopal symptoms. Against our expectations, CBFV fell to the same absolute level (in symptomatic subjects) during both the sham and active ITD trials upon transition from the squatting to standing posture. However, CBFV oscillations increased with active ITD breathing and were associated with a reduction in the severity of orthostatic symptoms in eight out of nine subjects.

Breathing through the ITD has previously been shown to increase CBFV in supine, resting humans (9) and cerebral perfusion in hemorrhaged pigs (30,31). Two studies have also demonstrated that ITD breathing during orthostasis attenuates the decrease in arterial blood pressure and alleviates presyncopal symptoms (5,18). However cerebral blood flow was not recorded during

TABLE II. FREQUENCY DOMAIN RESPONSES DURING THE SHAM ITD AND ACTIVE ITD TRIALS.

Variable	Sham ITD			Active ITD			Sham vs. Active
	Squat	Stand	*P*-Value	Squat	Stand	*P*-Value	*P*-Value (Stand vs. Stand)
Mean $CBFV_{HF}$, $cm \cdot s^{-2}$	1.6 ± 0.5	2.5 ± 0.9	0.695	2.7 ± 1.6	7.8 ± 2.6	0.043	0.002
Mean $CBFV_{LF}$, $cm \cdot s^{-2}$	4.0 ± 0.7	4.1 ± 0.9	0.970	8.5 ± 4.3	6.9 ± 2.4	0.447	0.375
Mean $CBFV_{HF}$ n.u.	0.24 ± 0.03	0.35 ± 0.06	0.254	0.23 ± 0.04	0.55 ± 0.08	0.004	0.001
Mean $CBFV_{LF}$ n.u.	0.76 ± 0.03	0.66 ± 0.06	0.254	0.77 ± 0.04	0.46 ± 0.08	0.004	0.001
Mean $CBFV_{TOTAL}$, $cm \cdot s^{-2}$	5.6 ± 1.1	6.6 ± 1.5	0.808	11.2 ± 5.8	14.7 ± 3.9	0.394	0.061
MAP_{HF}, $mmHg^2$	2.0 ± 0.9	2.9 ± 0.7	0.605	1.1 ± 0.3	7.0 ± 2.2	0.002	0.012
MAP_{LF}, $mmHg^2$	5.9 ± 0.8	7.0 ± 1.4	0.648	5.4 ± 0.6	11.6 ± 3.5	0.028	0.042
MAP_{HF} n.u.	0.19 ± 0.05	0.33 ± 0.09	0.139	0.15 ± 0.03	0.40 ± 0.07	0.015	0.419
MAP_{LF} n.u.	0.81 ± 0.05	0.67 ± 0.09	0.139	0.85 ± 0.03	0.60 ± 0.07	0.015	0.419
MAP_{TOTAL}, $mmHg^2$	7.9 ± 1.7	9.8 ± 1.3	0.505	6.5 ± 0.9	18.6 ± 4.2	< 0.001	0.005
MAP-CBFV-COH, a.u.	0.53 ± 0.04	0.67 ± 0.04	0.062	0.58 ± 0.05	0.74 ± 0.04	0.048	0.277
MAP-CBFV-TF_{LF}, $(cm \cdot s^{-1}) \cdot mmHg^{-1}$	0.60 ± 0.09	0.65 ± 0.08	0.693	0.83 ± 0.11	0.70 ± 0.08	0.348	0.610

Values are mean ± SE; ITD, inspiratory threshold device; CBFV, cerebral blood flow velocity; MAP, mean arterial pressure; HF, high frequency; LF, low frequency; n.u., normalized units; COH, coherence; a.u., arbitrary units; TF, transfer function.

these studies to ascertain the relationship between ITD breathing, cerebral blood flow, and the subjective reporting of orthostatic symptoms. In a recent study performed in our laboratory, we measured the effect of ITD breathing on CBFV and the reporting of symptoms with progressive central hypovolemia induced by lower body negative pressure (LBNP) (25). Breathing with the ITD reduced the reporting of symptoms, but did not protect the fall in CBFV. In agreement with the findings of the current study, however, the ITD elicited a significant increase in CBFV oscillations. This increase in oscillatory power appears to play a protective role in reducing the severity of orthostatic symptoms. While there has been some contention surrounding the argument that absolute cerebral perfusion is directly linked to symptoms (14,23,29,34), the increase in CBFV oscillations and reduction in symptom severity, now demonstrated in two independent studies, may be important in better understanding this relationship and elucidating the underlying mechanism.

HF power is predominantly influenced by respiration (2,4,11). The increases in HF oscillatory power in CBFV (mean, systolic, and diastolic $CBFV_{HF}$) and arterial pressure (SBP_{HF}, DBP_{HF}, and MAP_{HF}) in the current study may be associated with the rhythmic decreases in intrathoracic pressure induced by breathing on the active ITD (30). In previous studies, active ITD breathing elicited similar increases in mean $CBFV_{HF}$ and MAP_{HF} oscillations in the supine, resting posture (9) and during supine LBNP (25). In the latter study (25), ITD breathing reduced respiratory rate by 3 breaths/min, produced peak negative pressures of −12.2 ± 1.1 cm H_2O, and prolonged time of inspiration by 30% compared with sham ITD breathing during exposure to LBNP. These data, in combination with the findings of Yannopoulos et al. (30), who showed that reductions in endotracheal pressure induced by inspiratory resistance were directly transmitted to intracranial pressure in the hemorrhaging swine model, suggest that active ITD breathing may have also reduced intrathoracic and

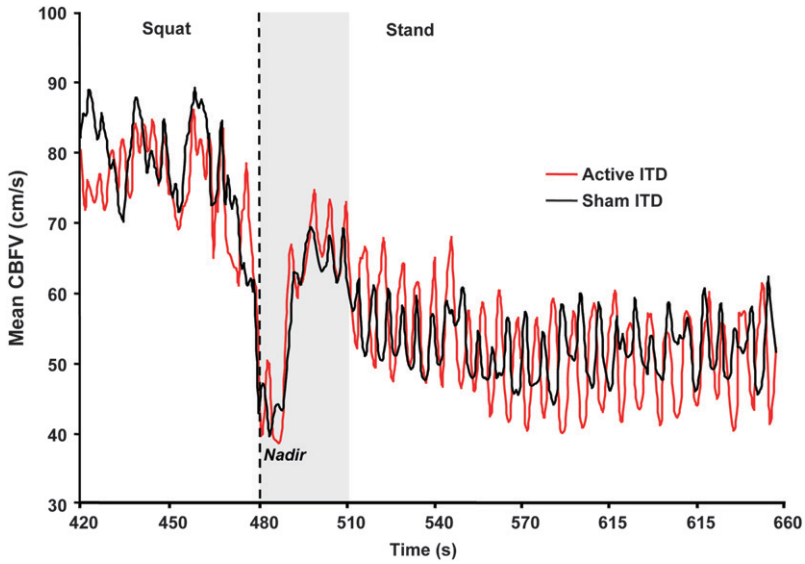

Fig. 3. A typical, representative tracing of mean cerebral blood flow velocity (CBFV) oscillations for one subject during the final 1 min of squat and first 3 min of stand during the sham ITD trial (black line) and the active ITD trial (red line). The dashed line represents the time of stand; the shaded area represents the first 30 s of stand when symptoms were reported. The nadir of CBFV occurs immediately following stand (i.e., at 480 s) under both conditions. For this subject, the absolute mean CBFV during the 3-min stand period for the sham ITD trial was 53.4 $cm \cdot s^{-1}$ and 53.5 $cm \cdot s^{-1}$ for the active ITD trial.

intracranial pressures in our subjects during the SST. The increase in arterial pressure oscillations at the breathing frequencies (associated with changes in intrathoracic pressure), may be directly transferred to CBFV, thereby accounting for the increase in CBFV HF oscillations we have now observed in three independent studies. Alternatively and/or additionally, reductions in intracranial pressure could increase the cerebral pressure gradient, thus promoting increased flow during each breath. However, as there are no published data (to our knowledge) to indicate either the effect of standing or ITD breathing on intracranial pressure in healthy humans, we can only speculate on this as a potential mechanism for the observed increase in CBFV oscillations.

The mechanism responsible for the improvement in symptomology with increases in HF oscillations is also presently unclear. Our data are consistent with the notion that active ITD breathing had no effect on cerebral autoregulation as determined by 1) similar coherence values between MAP and mean CBFV; 2) no difference in transfer function magnitudes among MAP and mean CBFV; 3) similar time to nadir and time to recovery responses for MAP and mean CBFV under both conditions; and 4) average R^2 values of < 0.75 between the responses of MAP and CBFV upon standing under both conditions. While there is no evidence to suggest that cerebral autoregulation was affected by ITD breathing, the oscillatory pattern of flow and the higher peak CBFV observed with ITD breathing (see Fig. 3) may enhance oxygen delivery to the brain, improving perfusion to regions associated with the reporting of orthostatic symptoms. Alternatively, the higher rhythmic oscillations in CBFV elicited with ITD breathing may increase sheer stress on the cerebral vessel walls (32). An increase in sheer stress may elicit the release of vasodilators, e.g., nitric oxide, or inhibit endothelin production, which would reduce cerebral vascular resistance and increase cerebral blood flow (26,32). It is unclear, however, whether vessel diameter or absolute cerebral blood flow changed with ITD breathing. Translating the measurement of CBFV to cerebral blood flow via the transcranial Doppler technique assumes a constant diameter of the MCA. While MCA diameter does not change during induced hypotension similar to the SST (19,27), we do not know the effect of breathing through an ITD on MCA diameter. We have previously proposed that the ITD-induced reduction in intracranial pressure (30,31) could increase MCA diameter and facilitate an increase in cerebral blood flow (25). However, there is no evidence that cerebral perfusion pressure was protected with ITD breathing in the current study, as MAP decreased under both the sham and active ITD conditions and we do not have measures of intracranial pressure. This further supports the contention that the CBFV oscillations alone may have provided protection from the onset of symptoms. It should also be noted, however, that limiting our measurements of blood flow velocity to the MCA alone cannot dismiss the possibility that the ITD affected local blood flow to other cerebral regions such as the brain stem. An assessment of vessel diameter, intracranial pressure changes, regional cerebral oxygenation (e.g., via near infrared spectroscopy), and isolating regions of enhanced cerebral blood flow and oxygenation (via functional magnetic resonance imaging) with ITD breathing would provide crucial information to further understand the relationship between enhanced oscillations in CBFV and cognitive function.

The finding that the ITD is effective in reducing the severity of orthostatic symptoms has important clinical implications. Every year approximately 1 million people are evaluated for syncope in the United States (29), a condition of reduced cerebral perfusion. The presence of symptoms with orthostatic hypotension can limit the freedom of movement and activity and reduce the quality of life in patients suffering from this condition. In a group of patients with orthostatic hypotension, breathing with the ITD attenuated the reduction in arterial blood pressure and alleviated orthostatic symptoms (18). Traditionally, absolute cerebral blood flow would be measured in the assessment of the relationship between cerebral perfusion and symptoms in these clinical disorders. As demonstrated in the representative tracing of CBFV responses to the SST in Fig. 3, however, mean CBFV was identical during both trials regardless of the presence of symptoms. More striking are the oscillations in CBFV with active ITD breathing, which are more regular, of greater amplitude and peak at higher velocities. An increase in HF oscillations, predominantly controlled by the pattern of breathing, may present a protective mechanism that can act to delay the onset of syncope, and may have potential implications for the treatment of clinical disorders associated with cerebral hypoperfusion, such as stroke. As the effect of the ITD is mechanical (i.e., a reduction in intrathoracic pressure) and does not require neural input, it also has potential utility in reducing debilitating orthostatic symptoms in patients with autonomic dysfunction.

There are a number of limitations associated with this study. First, we were not able to measure arterial CO_2, which has potent cerebral vasoactive properties (29). However, previous studies in our laboratory have shown that ITD breathing does not affect end tidal CO_2 (an imperfect predictor of arterial CO_2) in the supine, resting posture (9), and it decreases to the same level as with sham ITD breathing during progressive LBNP (25). Second, it is virtually impossible to "blind" subjects on whether they are using the sham or active ITD due to the mechanical effects of this device. Immediately upon inspiration, subjects are able to detect the increase in resistance present with the active ITD, so the reporting of less severe symptoms may have been biased. However, 10 of the original 19 subjects did not describe any difference in symptoms with either the sham or active ITD, so it is unlikely objective detection of resistance was a factor in the reduction of symptom severity in the symptomatic subjects. Additionally, this is now the fifth published study to describe the attenuation of symptoms with active ITD breathing associated with reductions in

central blood volume, all of which have demonstrated concomitant improvements in objectively measured cardiovascular function (5,6,18,25).

The findings of this study highlight the potential utility of ITD breathing in attenuating symptoms of orthostatic intolerance, which may be applicable to clinical populations with autonomic disorders and otherwise healthy individuals suffering from orthostatic hypotension following prolonged bed rest or spaceflight. Our results, based on retrospective selection of subjects with significant physiological compromise, underscore the potential for dismissing effective interventions by including populations that gain little benefit because of their uncompromised condition. Moreover, our analysis of CBFV oscillations rather than absolute mean CBFV alone provides unique insight into the relationship between cerebral perfusion and cognitive function.

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