Inspiratory resistance delays the reporting of symptoms with central hypovolemia: association with cerebral blood flow

Caroline A. Rickards,1 Kathy L. Ryan,1 William H. Cooke,2 Keith G. Lurie,3 and Victor A. Convertino1

1United States Army Institute of Surgical Research, Fort Sam Houston, Texas; 2Department of Health and Kinesiology, University of Texas at San Antonio, San Antonio, Texas; and 3Advanced Circulatory Systems, Inc., Department of Emergency Medicine at the University of Minnesota, and the Minneapolis Medical Research Foundation, Hennepin County Medical Center, Minneapolis, Minnesota

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Inspiratory resistance delays the reporting of symptoms with central hypovolemia: association with cerebral blood flow. Am J Physiol Regul Integr Comp Physiol 293: R243–R250, 2007. First published May 16, 2007; doi:10.1152/ajpregu.00087.2007.—We tested the hypothesis that breathing through an inspiratory threshold device (ITD) during progressive central hypovolemia would protect cerebral perfusion and attenuate the reporting of presyncopal symptoms. Eight human subjects were exposed to lower-body negative pressure (LBNP) until the presence of symptoms while breathing through either an active ITD (—7 cmH2O impedance) or a sham ITD (0 cmH2O). Cerebral blood flow velocity (CBFV) was measured continuously via transcranial Doppler and analyzed in both time and frequency domains. Subjects were asked to report any subjective presyncopal symptoms (e.g., dizziness, nausea) at the conclusion of each LBNP exposure. Symptoms were coincident with physiological evidence of cardiovascular collapse (e.g., hypotension, bradycardia). Breathing on the active ITD increased LBNP tolerance time (mean ± SE) from 2,014 ± 106 s to 2,259 ± 138 s (P = 0.006). We compared CBFV responses at the time of symptoms during the sham ITD trial with those at the same absolute time during the active ITD trial (when there were no symptoms). While there was no difference in mean CBFV at these time points (sham, 44 ± 4 cm/s vs. active, 47 ± 4; P = 0.587), total oscillations (sum of high- and low-frequency spectral power) of CBFV were higher (P = 0.004) with the active ITD (45.6 ± 10.2 cm/s^2) than the sham ITD (22.1 ± 5.4 cm/s^2). We conclude that greater oscillations around the same absolute level of mean CBFV are induced by inspiratory resistance and may contribute to the delay in symptoms and cardiovascular collapse that accompany progressive central hypovolemia.

Address for reprint requests and other correspondence: Caroline A. Rickards, U.S. Army Institute of Surgical Research, 3400 Rawley E. Chambers Ave., Bldg. 3611, Fort Sam Houston, TX 78234-6315 (e-mail: carolinerickards@hotmail.com).

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**Authors:** Rickards C. A., Ryan K. L., Cooke W. H., Lurie K. G., Convertino V. A.,
hemorrhage) in humans (13). With the use of a neoprone skirt designed to form an airtight seal between the subject and the chamber, the application of LBNP (below the iliac crest) results in a redistribution of blood away from the upper body (head and heart) to the abdomen and lower extremities. Thus, this model provides a unique method of investigating interventions, such as the ITD under conditions of controlled, experimentally-induced, hypovolemic hypotension.

All subjects were instrumented for the noninvasive, continuous measurement of HR via a standard ECG, and beat-to-beat arterial systolic (SBP) and diastolic (DBP) blood pressures via infrared finger plethysmography with a Finometer blood pressure monitor (TNO-TPD; Biomedical Instrumentation, Amsterdam, The Netherlands). An appropriately sized Finometer\textsuperscript{a} blood pressure cuff was placed on the middle finger of the left hand, which, in turn, was laid at heart level. Resting, supine blood pressure measurements were verified against a manual sphygmomanometer recording to validate Finometer readings. The difference between these two techniques was 1.2 ± 1.9% for SBP and 6.4 ± 1.8% for DBP.

The CBFV of the right middle cerebral artery (MCA) was recorded using a 2-MHz Doppler probe (EZ-Dop, DWL Elektronische Systeme, Sipplingen, Germany) positioned at a constant angle over the temporal window, located above the zygomatic arch. The transcranial Doppler (TCD) procedure for measuring CBFV has previously been described (1, 28). Briefly, the ultrasound signal emitted from the Doppler probe is reflected by 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 CBFV via fast Fourier transform analysis (1, 28, 29, 31). The resultant waveform (similar to a blood pressure waveform) is produced via spectral analysis of the blood flow velocity signal (28).

Each subject underwent exposure to an LBNP protocol designed to test their tolerance to experimentally induced hypotensive hypovolemia. The LBNP protocol consisted of a 5-min controlled rest period followed by 5 min of chamber decompression at -15, -30, -45, and -60 mmHg and additional increments of -10 mmHg every 5 min until the onset of cardiovascular collapse or the completion of 5 min at -100 mmHg. Cardiovascular collapse was defined by one or a combination of the following criteria: 1) a precipitous fall in SBP >15 mmHg and/or a sudden bradycardia, 2) progressive diminution of SBP below 70 mmHg, or 3) voluntary subject termination due to the onset of subjective presyncope symptoms such as gray-out, sweating, nausea, dizziness, or general discomfort. Each LBNP exposure represented a complete experimental session. Subjects completed three experimental sessions: 1) an initial protocol to determine LBNP tolerance without the application of any ITD, 2) during spontaneous breathing through a face mask with an ITD set at a resistance of approximately -7 cmH\textsubscript{2}O (active ITD), and 3) during spontaneous breathing through the same face mask using an ITD with no inspiratory resistance (sham ITD). Experimental sessions were separated by a minimum of 2 wk to avoid the possibility of increased LBNP tolerance due to multiple exposures (19, 20). The ITD devices (active or sham) were placed on the subjects at one LBNP level lower than the level that produced cardiovascular collapse during the initial tolerance protocol. For example, a subject who experienced cardiovascular collapse at -60 mmHg LBNP during the initial tolerance protocol would begin breathing on the sham or active ITD at -45 mmHg during the treatment experiment.\textsuperscript{1} Because the initial tolerance protocol was only used to determine when to place the ITD device, these data were not used in subsequent analyses for this report. The order of the two ITD treatments was randomized so that three of the subjects underwent testing during active ITD treatment first, and five of the subjects underwent testing with the sham ITD treatment first. All experimental protocols for a given subject were initiated at the same time of day.

Experimental intervention. The ITD is a small, light-weight, disposible plastic valce that was recently developed for treatment of a number of different clinical conditions associated with significant life-threatening hypotension (24, 26, 32, 33, 38). The ITD includes a specially designed valve that closes when the pressure within the thorax is less than atmospheric pressure and a second valve (termed the safety check valve) that opens at a preset negative intrathoracic pressure. In the spontaneously breathing subject, the ITD creates a small vacuum within the chest, drawing blood from the extrathoracic venous system into the heart each time the subject takes a breath (21, 22, 25). By increasing preload to the heart, the ITD results in an immediate increase in SBP and DBP (4, 5, 12, 21, 25) and a reduction in ICP with a subsequent increase in cerebral perfusion pressure (40) and CBFV (12). Inspiratory and expiratory pressures were recorded directly from the ITD using a commercial pressure transducer (MKS Instruments, Andover, MA) connected to the face mask, and end-tidal CO\textsubscript{2} was measured on a breath-by-breath basis as subjects breathed through the mask (BCI Capnocheck Plus; Smiths Medical, Waukesha, WI).

Data analysis. Continuous, beat-to-beat ECG, Finometer and Doppler, and breath-to-breath end-tidal CO\textsubscript{2} and ITD pressure recordings were sampled at 500 Hz and recorded directly to a computer-based data acquisition software package (WinDAQ, Daga Instruments, Akron, OH). R waves generated from the ECG signal were detected and marked at their occurrence in time. DBPs, SBPs, and diastolic and systolic flow velocities were subsequently marked from the Finometer and Doppler tracings, respectively. Using the arterial pressure waveform as an input, SV was estimated on a beat-by-beat basis using the pulse contour method outlined by Jansen et al. (17) and Q was estimated by multiplying SV by HR; mean arterial pressure (MAP) was calculated via the equation, MAP = DBP + 1/3(SBP – DBP). Mean CBFV was calculated as: mean CBFV = diastolic CBFV + 0.4(systolic CBFV – diastolic CBFV) from the CBFV waveform.

All time and frequency domain variables were calculated from the final 3 min of the baseline period (T1) under each ITD condition. To uncover the physiological mechanisms underlying the protective effect of ITD breathing during exposure to LBNP, the time point of cardiovascular collapse during the sham ITD trial was first identified for each subject; this time point was designated T2 (see Fig. 1). Data were then analyzed for both the sham and active ITD trials using this absolute time as the reference point. To capture the dynamic responses at cardiovascular collapse, all time domain variables were calculated from the 10 heart beats of data immediately preceding T2; the only exceptions were end-tidal CO\textsubscript{2} and respiratory rate, which were calculated from the final 1 min of data preceding T2, as 10 heart beats were not sufficient to accurately calculate these variables. For frequency domain variables, the final 3 min of data prior to T2 were analyzed under both ITD conditions.

Oscillatory patterns of arterial blood pressures and CBFVs 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. Three-minute data sets were fast Fourier transformed with a Hanning window to obtain power spectra. Spectral power was expressed as the integrated area within the low-frequency (LF = 0.04 to 0.15 Hz) and high-frequency (HF = 0.15 to 0.4 Hz) ranges.

We calculated the coherence among MAP and mean CBFV by dividing the cross-spectral densities of the two signals by the product of the individual autospectra. 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 (42). 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.

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A paired Student’s t-test was used to compare the sham ITD and active ITD LBNP tolerance times. A two-way (time, T1 and T2; ITD condition, active and sham) analysis of variance for repeated measures was used for comparison of all physiological variables, followed by Tukey’s post hoc tests. All data are presented as means ± SE and exact P values are presented for all comparisons.

RESULTS

Of the 16 trials (8 active ITD, 8 sham ITD), only one subject (during the active ITD trial) completed the LBNP protocol to 100 mmHg. As previously reported (10), breathing on the sham ITD did not increase LBNP tolerance time compared with the initial LBNP tolerance trial, indicating there was no sham effect. Breathing on the active ITD increased LBNP tolerance time from 2,014 ± 106 s with the sham ITD to 2,259 ± 138 s (P = 0.006). There was no difference in any of the baseline (T1) time or frequency domain variables between the active and sham ITD trials (P ≥ 0.456) (Table 1). Figure 1 is a representative tracing of the mean CBFV response during the final 3 min of the sham ITD trial (T2) and at the same absolute time during the active ITD trial (T2).

At T2, when subjects were breathing on the sham ITD, mean CBFV had decreased by 37 ± 5% from 69 ± 4 cm/s to 44 ±

Table 1. Time domain data at T1 and T2 during the sham ITD and active ITD trials

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sham ITD</th>
<th>Active ITD</th>
<th>Sham vs. Active</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
<td>T2</td>
<td>P Value (T1 vs. T2)</td>
</tr>
<tr>
<td>Systolic CBFV, cm/s</td>
<td>95±4</td>
<td>71±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic CBFV, cm/s</td>
<td>51±4</td>
<td>31±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean CBFV, cm/s</td>
<td>69±4</td>
<td>44±4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>92±4</td>
<td>59±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Q, l/min</td>
<td>5.3±0.3</td>
<td>3.5±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>End-tidal CO₂, mmHg</td>
<td>39.3±0.7</td>
<td>25.8±2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>14±1</td>
<td>15±2</td>
<td>0.398</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 8 subjects. T1, baseline; T2, absolute time point of presyncope during sham trial; ITD, inspiratory threshold device; CBFV, cerebral blood flow velocity; MAP, mean arterial pressure; Q, cardiac output.

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Statistical analysis. A paired Student’s t-test was used to compare the sham ITD and active ITD LBNP tolerance times. A two-way (time, T1 and T2; ITD condition, active and sham) analysis of variance for repeated measures was used for comparison of all physiological variables, followed by Tukey’s post hoc tests. All data are presented as means ± SE and exact P values are presented for all comparisons.
4 cm/s ($P < 0.001$). At the same absolute time during the active ITD trial (when there were no symptoms), mean CBFV had fallen to a similar level of $47 \pm 4$ cm/s from $68 \pm 6$ cm/s at rest ($P < 0.001$), a drop of $30 \pm 2\%$ (Table 1). While there was no apparent difference in absolute mean CBFV between the two conditions ($P = 0.587$), analysis of cerebral oscillations identified significant effects of ITD breathing (Fig. 1). Breathing through the active ITD increased both HF and LF oscillations, and subsequently total oscillations (the sum of LF and HF power) in mean CBFV at T2 (Fig. 2A and Table 2), coincident with an absence of symptoms. This increase in total oscillatory power with active ITD breathing was more than twofold greater than at the same time during the sham ITD trial ($P = 0.004$).

Mean CBFV decreased by $37\%$ in relative proportion to the reduction in estimated $Q$ of $35\%$ during the sham trial to presyncope (Fig. 3). In comparison, CBFV decreased by $30\%$ at T2, despite only a $12\%$ reduction in $Q$ when subjects were breathing on the active ITD (Fig. 3). Additionally, at T2 there was no change in MAP when subjects were breathing on the active ITD ($P = 0.473$) compared with a $36\%$ decrease from baseline ($P < 0.001$) when subjects were breathing on the sham ITD. This maintenance of MAP with active ITD breathing was associated with increases in LF and total oscillations in MAP compared with the sham trial (Fig. 2B and Table 2).

Analysis of transfer magnitudes among MAP and mean CBFV at the LF revealed an effect of active ITD breathing on dynamic cerebral autoregulation at T2 compared with T1 (T1, $0.9 \pm 0.1$ cm$\cdot$s$^{-1} \cdot$mmHg$^{-1}$ vs. T2, $0.6 \pm 0.1$ cm$\cdot$s$^{-1} \cdot$mmHg$^{-1}$; $P = 0.009$). However, at T2 there was no difference between the active and sham ITD trials (sham ITD, $0.7 \pm 0.1$ cm$\cdot$s$^{-1} \cdot$mmHg$^{-1}$ vs. active ITD, $0.6 \pm 0.1$ cm$\cdot$s$^{-1} \cdot$mmHg$^{-1}$; $P = 0.482$).

Progressive LBNP elicited reductions in end-tidal CO$_2$ under both the sham ($-13.4 \pm 2.9$ mmHg, $P < 0.001$) and active ITD ($-17.9 \pm 1.9$ mmHg, $P < 0.001$) conditions, but there was no difference between conditions (Table 1). Breathing through the active ITD elicited a decrease in respiration frequency from $14 \pm 1$ breaths/min at T1 to $11 \pm 1$ breaths/min at T2 ($P = 0.029$). This rate of breathing was lower than during the sham ITD trial ($P = 0.007$).
DISCUSSION

We hypothesized that breathing through an active ITD during progressive central hypovolemia induced by LBNP would delay the onset of presyncope sympotms and increase tolerance by attenuating the fall in cerebral blood flow. In partial support of our hypothesis, LBNP tolerance increased and presyncope symptoms were delayed by 4 min (245 s) when subjects breathed on the active ITD. Unexpectedly, however, this protective effect was not associated with the maintenance of CBFV.

Previous investigations have revealed that spontaneously breathing on the active ITD is associated with elevations in mean CBFV in passive, supine humans (12), and cerebral perfusion pressure in pigs following significant (35–50%) hemorrhage (40, 41). While subjective symptoms of presyncope cannot be ascertained with an animal model of hemorrhage, breathing on the active ITD attenuated the reporting of symptoms during the hypotensive challenge of the squat-stand test in human subjects (8), and in patients with orthostatic hypotension (27). However, neither ICP nor cerebral blood flow were recorded during these two studies to determine whether the reduction in symptoms was related to cerebral perfusion. We therefore hypothesized that the delay in presyncope symptoms in the current study would be associated with protection of mean CBFV. Unexpectedly, mean CBFV decreased to the same absolute level during both the sham and active ITD trials.

Fig. 3. The linear regression between the %change from baseline in cardiac output (Q) and mean CBFV during the sham ITD (white circles, dashed line) and active ITD (black circles, solid line) trials. Each point represents the group average for %change in Q and CBFV at 20, 40, 60, 80, and 100% of maximum tolerated lower-body negative pressure (means ± SE).

Table 2. Frequency domain data at T1 and T2 for the sham ITD and active ITD trials

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sham ITD</th>
<th>Active ITD</th>
<th>Sham vs. Active</th>
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<tbody>
<tr>
<td></td>
<td>T1</td>
<td>T2</td>
<td>P Value (T1 vs. T2)</td>
</tr>
<tr>
<td>Mean CBFV&lt;sub&gt;HF&lt;/sub&gt;, cm/s&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1.3±0.4</td>
<td>13.1±3.8</td>
<td>0.083</td>
</tr>
<tr>
<td>Mean CBFV&lt;sub&gt;LF&lt;/sub&gt;, cm/s&lt;sup&gt;2&lt;/sup&gt;</td>
<td>6.5±1.6</td>
<td>9.0±2.4</td>
<td>0.668</td>
</tr>
<tr>
<td>Mean CBFV&lt;sub&gt;TOTAL&lt;/sub&gt;, cm/s&lt;sup&gt;2&lt;/sup&gt;</td>
<td>7.9±1.6</td>
<td>22.1±5.4</td>
<td>0.099</td>
</tr>
<tr>
<td>MAP&lt;sub&gt;HF&lt;/sub&gt;, cmHg</td>
<td>1.1±0.2</td>
<td>12.3±5.0</td>
<td>0.013</td>
</tr>
<tr>
<td>MAP&lt;sub&gt;LF&lt;/sub&gt;, cmHg</td>
<td>6.3±1.3</td>
<td>14.2±4.7</td>
<td>0.395</td>
</tr>
<tr>
<td>MAP&lt;sub&gt;TOTAL&lt;/sub&gt;, cmHg</td>
<td>7.3±1.3</td>
<td>26.5±7.1</td>
<td>0.066</td>
</tr>
<tr>
<td>MAP-CBFV&lt;sub&gt;-TF&lt;/sub&gt;, cm·s&lt;sup&gt;-1&lt;/sup&gt;·mmHg&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>0.8±0.1</td>
<td>0.7±0.1</td>
<td>0.482</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 8 subjects. HF, high frequency; LF, low frequency; TF, transfer function.

With the known relationship between Q and CBFV, this 12% reduction in Q while breathing on the active ITD should have elicited a fall in CBFV of 8 cm/s. Instead, CBFV was reduced by 21 cm/s with the active ITD, more than double the predicted value. One of two possible conclusions emerges from these findings. First, an unlikely explanation is that the relative magnitude of reduction in cerebral blood flow was similar to the same absolute level during both the sham and active ITD trials. However, a number of factors indicate that breathing on the active ITD may have protected absolute cerebral blood flow (i.e., maintained cerebral autoregulation) during progressive central hypovolemia despite the reduction in CBFV.

Ogoh et al. (30) and Van Lieshout et al. (36) have clearly demonstrated that maintaining a higher Q is associated with an elevated CBFV under conditions of rest, orthostasis, and exercise. In agreement with these findings, we found a directly proportional relationship between the changes in Q and CBFV with progressive LBNP during the sham ITD trial. As the LBNP stimulus was, by design, exactly the same during the two ITD conditions, we expected any relative change in CBFV to be directly proportional to the relative change in Q at T2 while breathing on the active ITD. However, against expectations, we found that a 30% reduction in CBFV was associated with only a 12% fall in Q.

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between the sham and active ITD conditions, suggesting that cerebral blood flow has no relationship with symptoms. A more likely possibility is that CBFV during active ITD breathing does not reflect the relative protection of cerebral blood flow as a result of the changing diameter of the MCA and a subsequent reduction in resistance. Although the MCA diameter does not change during LBNP alone (35), we do not know the effect of breathing through an ITD on MCA dimensions (a fundamental assumption and limitation of the measurement of cerebral blood flow by TCD). As there are data that indicate that breathing on an active ITD decreases ICP (40, 41), it is possible that a more negative ICP (the vacuum effect) could increase MCA diameter. In this scenario, breathing on the active ITD could result in higher cerebral blood flow compared with the sham ITD despite similar reductions in CBFV. Thus, the combination of reducing ICP (40, 41) and increasing perfusion pressure (40) provides a possible mechanism for the ITD to protect cerebral autoregulation and delay the onset of symptoms during progressive central hypovolemia.

Our data are the first to suggest the possibility that the measurement of CBFV and the calculated cerebrovascular resistance index may not be accurate indexes of flow or resistance under the condition of active ITD breathing. As such, the 10% increase in CBFV reported in a previous investigation conducted in our laboratory in supine, resting subjects (12) may have been an underestimation. Clearly, measures of absolute cerebral blood flow and/or cerebral vessel diameter with ITD breathing are required to confirm these hypotheses and to further elucidate the physiological mechanism underlying the protective effect of the ITD under conditions of hypovolemic stress.

During ITD breathing there are three key effects associated with central hemodynamics; a decrease in intrathoracic pressure (26), an increase in arterial pressure oscillations (Table 2), and the protection of Q (8, 9). At the cerebral level, there are similar decreases in ICP (40), and we have now presented evidence in this investigation to indicate increases in CBFV oscillations (Table 2). These similar responses in oscillations and pressure between the cerebral and cardiac compartments provide indirect evidence for the notion that cerebral blood flow may have been protected with ITD breathing in parallel with Q during progressive central hypovolemia in the present study.

CBFV oscillations were twofold greater in both the HF and LF domains with active ITD breathing. As demonstrated in the representative tracing (Fig. 1) oscillations during active ITD breathing were more regular, of greater amplitude, and peaked at higher velocities compared with the sham ITD. Although LBNP alone can elicit increases in cerebral blood flow oscillations (43), this effect was not statistically robust in the current study. However, breathing on the active ITD optimized this oscillatory pattern. Our results present the hypothesis that regular fluctuations of cerebral blood flow into higher maximum velocities with active ITD breathing may represent a protective mechanism for maintaining adequate cerebral perfusion that delays the onset of presyncopeal symptoms and prolongs tolerance to LBNP. To our knowledge this is the first time that oscillations in CBFV have been potentially linked to cognitive function in the setting of progressive hypovolemia and hypotension. This mechanism may have clinical implications for the development of methods to protect patients from hypotension, stroke, and other disorders associated with cerebral hypoperfusion.

The increase in total oscillatory power with active ITD breathing observed in the present study resulted from increases in oscillations in both the HF and LF domains (Fig. 2 and Table 2). As with R-R interval spectral power and arterial blood pressure, LF oscillations in CBFV are associated with sympathetic modulation of this vascular bed (3). In the resting, supine posture breathing through the active ITD did not elicit an increase in directly measured muscle sympathetic nerve activity (MSNA), nor was there an increase in mean CBFVLF (12). Application of progressive LBNP and the reduction in central blood volume, however, does elicit increases in both MSNA (7, 15, 34) and mean CBFVLF (43). Interestingly, in the current study, LBNP alone (sham ITD trial) did not increase CBFVLF, but the combined effect of LBNP and active ITD breathing elevated CBFVLF by 209%. It is possible that the LF oscillations in CBFV were not elevated at T2 during the sham trial as subjects had reached presyncope, which can be associated with sympathetic withdrawal (11). By comparison, at T2 during the active ITD trial, subjects had not yet reached presyncope, so sympathetic activity might still be elevated and may be reflected in an increase in LF oscillations.

As HF power is predominantly influenced by respiration (2, 3, 14), the increases in HF oscillatory power from baseline in both arterial pressure (MAPΔhp) and CBFV (mean CBFVHF) may be associated with the rhythmic decreases in intrathoracic pressure and ICP induced by breathing on the active ITD (40). Active ITD breathing reduced respiratory rate by 3 breaths/min, produced peak negative pressures of −12.2 ± 1.1 cmH2O and prolonged time of inspiration by 30% compared with sham ITD breathing (10). While we do not have direct recordings of intrathoracic pressure, these data suggest that active ITD breathing further reduced negative intrathoracic pressure and prolonged the time at negative pressure for each breath compared with breathing on the sham ITD. Based on the findings of Yannopoulos et al., (40) where reductions in endotracheal pressure with ITD breathing were directly transmitted to ICP in the hemorrhaging swine model, we postulate that the rhythmic oscillations in CBFV in the HF domain are associated with breath-dependant oscillations in intrathoracic pressure and ICP.

Zhang et al. (43) contend that increases in the variability of arterial pressure with LBNP drive the simultaneous changes in CBFV, representing the attenuation of cerebral autoregulation. However, the maintenance of cerebral autoregulation with LBNP alone (sham ITD trial) and the improvement in cerebral autoregulation with LBNP and active ITD breathing (as indicated by a decrease in gain of the transfer function between MAP and CBFV), suggest that while both arterial blood pressure and CBFV displayed significant increases in oscillatory power, there is an independence of cerebral oscillations from arterial blood pressure oscillations. This finding is supported by Cencetti et al. (3) who demonstrated a phase delay between LF oscillations in cerebral blood flow and subsequent oscillations in arterial blood pressure during head-up tilt, suggesting that the cerebral oscillations originate in the cerebral circulation and do not result from the passive transmission of oscillations in arterial blood pressure. In contrast to the hypothesis that the increase in cerebral oscillations with central hypovolemia represents an attenuation of cerebral autoregula-

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tion which contributes to syncope (43), our results suggest that these oscillations may actually represent a protective mechanism that protects cerebral autoregulation and can act to delay the onset of syncope.

A terminal end-point during exposure to LBNP is the onset of presyncope symptoms that often precedes cardiovascular collapse. Breathing on an inspiratory resistance device delayed the onset of symptoms with an associated increase in tolerance to progressive central hypovolemia. The mechanical effects of ITD breathing elevated both HF and LF oscillations in CBFV, and may have protected absolute cerebral blood flow. The increase in oscillatory power in both arterial blood pressure and CBFV may be associated with a protective effect against the development of hypotension and the onset of cardiovascular decompensation. The effect of ITD breathing on cerebral blood flow and vessel dimensions requires further investigation to elucidate the relationship between cognitive function, cerebral blood flow, and oscillations. Our results underscore the usefulness of enhancing the respiratory pump as an intervention for delaying the onset of circulatory shock in hemorrhaging patients.

ACKNOWLEDGMENTS

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Dr. Keith Lurie is a coinventor of the impedance threshold device, founded Advanced Circulatory Systems Inc. to develop the device, and will benefit from sale of the device. There are no other conflicts of interest.

REFERENCES


