

Breathing through an inspiratory threshold device improves stroke volume during central hypovolemia in humans

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

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

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Ryan KL, Cooke WH, Rickards CA, Lurie KG, Convertino VA. Breathing through an inspiratory threshold device improves stroke volume during central hypovolemia in humans. *J Appl Physiol* 104: 1402–1409, 2008. First published February 28, 2008; doi:10.1152/jappphysiol.00439.2007.—Inspiratory resistance induced by breathing through an impedance threshold device (ITD) reduces intrathoracic pressure and increases stroke volume (SV) in supine normovolemic humans. We hypothesized that breathing through an ITD would also be associated with a protection of SV and a subsequent increase in the tolerance to progressive central hypovolemia. Eight volunteers (5 men, 3 women) were instrumented to record ECG and beat-by-beat arterial pressure and SV (Finometer). Tolerance to progressive lower body negative pressure (LBNP) was assessed while subjects breathed against either 0 (sham ITD) or -7 cmH₂O inspiratory resistance (active ITD); experiments were performed on separate days. Because the active ITD increased LBNP tolerance time from $2,014 \pm 106$ to $2,259 \pm 138$ s ($P = 0.006$), data were analyzed (time and frequency domains) under both conditions at the time at which cardiovascular collapse occurred during the sham experiment to determine the mechanisms underlying this protective effect. At this time point, arterial blood pressure, SV, and cardiac output were higher ($P \leq 0.005$) when breathing on the active ITD rather than the sham ITD, whereas indirect indicators of autonomic activity (low- and high-frequency oscillations of the R-to-R interval) were not altered. ITD breathing did not alter the transfer function between systolic arterial pressure and R-to-R interval, indicating that integrated baroreflex sensitivity was similar between the two conditions. These data show that breathing against inspiratory resistance increases tolerance to progressive central hypovolemia by better maintaining SV, cardiac output, and arterial blood pressures via primarily mechanical rather than neural mechanisms.

lower body negative pressure; hypotension; inspiratory resistance

ONE OF THE CHALLENGES TO EFFECTIVE management of hypovolemic hypotension is maintenance of vital organ perfusion when intravenous access and fluids, drug therapies, and surgical intervention are not readily available (41, 42). The impedance threshold device (ITD) was developed to provide just such a “bridge” between the sites of injury and definitive care by exploiting and amplifying basic physiological mechanisms that occur during normal inspiration. That is, intrathoracic pressure decreases during inspiration, resulting in a decrease in atrial pressure and increases in venous return and stroke volume (SV) (2). Breathing through the ITD amplifies this normal respiratory pump by providing resistance during spontaneous inspiration, which further decreases intrathoracic pressure and

thereby produces greater increases in venous return, ventricular preload, and cardiac output (\dot{Q}) (6, 31). Our laboratory has previously demonstrated that spontaneous breathing through an ITD increases SV, \dot{Q} , and arterial blood pressure in healthy normovolemic, normotensive humans, suggesting that its use might also be helpful in hypovolemic situations (12, 15). Indeed, use of the ITD decreased right atrial pressure, and increased \dot{Q} , systemic arterial blood pressure, and survival in anesthetized pigs undergoing hemorrhage (33, 35, 43, 51, 52), and produced similar protective effects in conscious humans made hypotensive by orthostatic challenges (9, 10).

While the ITD has been shown to be protective of SV and \dot{Q} , it is possible that alterations in autonomic function might also contribute to the maintenance of blood pressure during resistive breathing, as previously suggested (3). In normovolemic, normotensive humans, however, ITD breathing increases arterial blood pressure without producing increases in sympathetic nerve activity (15). Furthermore, the gain of the carotid baroreflex in resting human subjects is not altered by use of the ITD, although the set point is reset toward higher arterial pressures (11). A systematic examination of autonomic function during ITD breathing has not yet been undertaken in human subjects under conditions of central hypovolemia, in which increased sympathetic activation is already present.

Our laboratory recently reported that an increase in tolerance to progressive central hypovolemia using inspiratory resistance was associated with maintenance of blood pressure (13) and delayed onset of symptoms (39). We now report physiological mechanism(s) associated with these protective outcomes in a subset of these same subjects. We used a graded protocol of lower body negative pressure (LBNP) to the point of cardiovascular collapse (i.e., presyncope) as a surrogate for severe hemorrhage (17, 46) to test the hypothesis that the increase in tolerance to progressive central hypovolemia and protection of blood pressure (13) provided by use of the ITD is accomplished by protection of SV and \dot{Q} . We further hypothesized that maintenance of blood pressure would be accomplished primarily through a mechanical effect on central hemodynamics without significant contribution from peripheral neural autonomic mechanisms.

MATERIALS AND METHODS

Subjects. Five male and four female (age 31 ± 2 yr; height 173 ± 2 cm; weight 77 ± 4 kg) nonsmoking subjects volunteered to participate in this study. All experimental procedures were approved

Address for reprint requests and other correspondence: K. L. Ryan, US Army Institute of Surgical Research, Bldg. 3611, 3400 Rawley E. Chambers Ave., Fort Sam Houston, TX 78234-6315 (e-mail: kathy.ryan@amedd.army.mil).

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by the Institutional Review Board of the Brooke Army Medical Center (Fort Sam Houston, TX). Before inclusion, all subjects underwent a medical history and physical examination by a physician to ensure that they had no previous or current medical conditions that might preclude their participation. In addition, female subjects underwent a urine pregnancy test within 24 h of experimentation. Subjects were instructed to maintain their normal sleep patterns, refrain from exercise, and abstain from caffeine and other autonomic stimulants, including prescription or nonprescription drugs, for at least 24 h before the study. Subjects received a verbal briefing and written descriptions of all procedures and risks associated with the study, and they were made familiar with the laboratory, the protocol, and procedures. Subjects were encouraged to ask questions of the investigators, and then gave their written informed consent to participate in the study.

Experimental intervention. The ITD (Advanced Circulatory Systems, Inc., Eden Prairie, MN) is a small lightweight disposable plastic airway pressure regulator that can be attached to a face mask or other airway adjunct. The ITD includes an expiratory valve that closes when the proximal airway pressure is less than atmospheric pressure and a second inspiratory valve that opens at a preset negative face mask pressure of approximately -7 cmH₂O. The ITD was designed to generate a negative inspiratory threshold pressure and to therefore generate substantially more negative intrapleural pressure during spontaneous inhalation (7, 33). There is little resistance (<2 cmH₂O) during exhalation. An ITD set at -7 cmH₂O was chosen because this level has been previously shown to be tolerable and effective in increasing arterial blood pressures in human volunteers (9–13, 15). Inspiratory and expiratory pressures were recorded directly from the ITD using a commercial pressure transducer (All Sensors, Morgan Hill, CA) connected to the face mask and have been reported elsewhere (13).

Experimental protocol. Subjects were instrumented with a standard four-lead electrocardiogram to record cardiac electrical potentials and with an infrared finger photoplethysmograph (Finometer Blood Pressure Monitor, TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands) to record beat-by-beat finger arterial pressure. The Finometer blood pressure cuff was placed on the middle finger of the left hand, which in turn was laid at heart level. End-tidal CO₂ was monitored on a breath-by-breath basis as subjects exhaled into a face mask (BCI Capnocheck Plus, Smiths Medical, Waukesha, WI), and it was used to derive respiratory rate.

Central hypovolemia was induced by application of LBNP to simulate, as closely as possible in healthy human volunteers, the hemodynamic challenges associated with severe hemorrhage (17). Subjects were placed in the supine position within an airtight chamber and sealed at the level of the iliac crest by way of a neoprene skirt. Each subject underwent exposure to an LBNP protocol designed to test their LBNP tolerance. The LBNP protocol consisted of a 5-min rest period (baseline) followed by 5 min of chamber decompression at -15 , -30 , -45 , and -60 mmHg, and then 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 systolic blood pressure >15 mmHg; 2) a sudden bradycardia; 3) progressive diminution of SBP below 70 mmHg; and 4) voluntary subject termination due to discomfort from symptoms such as grayout, sweating, nausea, or dizziness. Each LBNP protocol 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) exposure to the LBNP protocol while spontaneously breathing through a face mask with an ITD set at a resistance of approximately -7 cmH₂O (active ITD); and 3) exposure to the LBNP protocol while spontaneously breathing through the same face mask and an ITD without inspiratory resistance (sham ITD). The experimental sessions were each separated by a minimum of 2 wk to avoid the possibility of increased LBNP

tolerance due to multiple exposures (29, 30). Intraindividual reliability assessment of LBNP tolerance time (as assessed from the baseline and sham trials) in these subjects yielded a coefficient of variation of 12.9%; the average LBNP tolerance times between the baseline ($1,921 \pm 138$ s) and sham ($2,014 \pm 106$ s) trials were not statistically different ($P = 0.45$). During the ITD protocols, the ITD devices were placed on the subjects at one LBNP level less negative than that which produced cardiovascular collapse during the initial tolerance protocol. For example, a subject who experienced cardiovascular collapse at -70 mmHg LBNP during the initial tolerance protocol would begin breathing on the sham or active ITD at -60 mmHg during each of the two treatment experiments. 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. Subsequently, the order of the two ITD treatments was randomized such that five of the subjects underwent testing with the sham ITD treatment first, while four subjects received the active ITD first. As much as possible, subjects were blinded to which ITD treatment they received in each experiment; because of the resistance to breathing afforded by the active ITD, however, it was impossible to completely blind the subject once ITD breathing commenced. Similarly, the experimental condition was readily apparent to the investigators once the ITD was placed as real-time measurement of inspiratory pressures were being recorded. All experimental protocols for a given subject were initiated at the same time of day.

As reported previously (13), LBNP tolerance time was increased during the active ITD trial in eight of the nine subjects but was not changed in one subject. The inability of the ITD to increase tolerance in this one subject was probably because inspiratory pressures were not decreased and sustained sufficiently to provide benefit in this subject (13). Because the question addressed herein concerns the physiological mechanisms underlying the protective effect of ITD breathing on increasing LBNP tolerance, we chose to only analyze and report data obtained from the eight subjects in whom a protective effect was evident.

Data analysis. Data were sampled at 500 Hz, digitized to computer (WinDAQ, Dataq Instruments, Akron, OH), and then imported into commercially available data analysis software (WinCPRS, Absolute Aliants, Turku, Finland). Individual R waves generated from the ECG were marked at their occurrence in time and used for subsequent identification of systolic and diastolic pressures generated from the Finometer. 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. (25). \dot{Q} was estimated by multiplying SV and heart rate.

Data were analyzed in both time and frequency domains. For representation in the frequency domain, R-to-R intervals (RRI) and arterial pressures were replotted using linear interpolation and resampled at 5 Hz. Data then were passed through a low-pass impulse-response filter with a cutoff frequency of 0.5 Hz. Data sets were analyzed in the frequency domain using a Fourier transform with a Hanning window. Signal areas were separated into high-frequency (0.15–0.4 Hz) and low-frequency (0.04–0.15 Hz) bands (28). The coherence existing between systolic pressure and RRI was calculated by dividing the cross-spectral densities of the two signals by the product of the individual autospectra. The transfer function (TF) magnitude was then calculated by dividing the cross-spectrum of systolic pressure and RRI by the autospectrum of systolic pressure (14). TF magnitude was averaged in the LF band only within those frequency ranges where the squared coherence was at least 0.5, and it was used as an estimate of integrated baroreflex sensitivity (18).

To directly measure sympathetic activity, we attempted to record muscle sympathetic nerve activity (MSNA) in all subjects as described previously (8). Although we were successful in obtaining baseline nerve recordings in most of the experiments (12 of 16), the high LBNP levels dislodged the recording electrode in most of these, and so we only have complete data sets across both experimental

conditions in one subject. In lieu of this, we used alterations of heart period variability within the low-frequency (RRI_{LF} ; 0.04–0.15 Hz) and high-frequency (RRI_{HF} ; 0.15–0.4 Hz) bands of the power spectrum as approximations of sympathetic and parasympathetic activation (16, 37).

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 LBNP exposure, the time point of presyncope during the sham ITD session was first identified for each subject; this time point was designated T2, as described previously (39). Data were then analyzed for both ITD conditions using this absolute time as the reference point for measurement. To capture the dynamics of presyncopal occurrences, all time domain variables were calculated from the 10 heartbeats of data immediately preceding T2; the only exceptions were end-tidal CO_2 and respiratory rate, which were calculated from the final 1 min of data preceding T2, because 10 heartbeats were not sufficient to accurately calculate these variables. For frequency domain variables (i.e., TF), the last 3 min of data before T2 were extracted for analysis.

Statistical analysis. Analysis was accomplished using commercially available software (SigmaStat, Systat Software, Richmond, CA). A *t*-test statistic for paired measures was used to compare the sham ITD and active ITD LBNP tolerance times. A two-way (time and ITD condition) analysis of variance for repeated measures was used for comparison of all other variables, followed by Tukey post hoc tests where appropriate. The probabilities of observing chance effects on the dependent variables of interest are presented as exact *P* values. All data are expressed as means \pm SE.

RESULTS

At baseline (T1), all time and frequency domain variables were similar ($P \geq 0.337$) between the two experimental sessions with the exception of SV, which was lower during the active ITD session ($P = 0.003$). Breathing on the active ITD increased LBNP tolerance time by 12%, from $2,014 \pm 106$ s (sham) to $2,259 \pm 138$ s ($P = 0.006$).

Time domain hemodynamic data are shown in Table 1 and Fig. 1. There were no statistical differences in hemodynamic variables between the two experimental conditions before placement of the sham or active ITD (Fig. 1). As expected, LBNP decreased RRI systolic and diastolic arterial pressures, mean arterial pressure, SV, and \dot{Q} in the sham ITD condition at cardiovascular collapse (T2; Fig. 1). Breathing on the active ITD, however, attenuated the decreases in arterial pressures, SV, and \dot{Q} produced by LBNP. Specifically, LBNP produced decreases in both SV ($-64 \pm 3\%$) and \dot{Q} ($-35 \pm 5\%$) at T2 during the sham ITD trial; at this same point during the active

ITD trial, these changes were reduced (SV, $-54 \pm 1\%$; \dot{Q} , $-11 \pm 4\%$; $P \leq 0.003$). The protective effect of the active ITD on \dot{Q} was accomplished solely via an improvement in SV, because heart rate increased similarly under both ITD conditions (Table 1). As a consequence of the attenuation of the decrease in \dot{Q} , the average reduction in mean arterial pressure at T2 with the active ITD (4 ± 2 mmHg) was less ($P < 0.006$) than that under the sham condition (33 ± 7 mmHg; Fig. 1). In addition to effects on hemodynamic parameters, spontaneous breathing on the active ITD also produced a decrease in respiratory rate during LBNP that was not observed during the sham ITD trial (Table 1).

Figure 2 depicts responses immediately before T2 in the one subject for whom we have complete MSNA recordings. In this one subject, MSNA was increased during LBNP exposure as evidenced by increases in burst frequency (from baseline values of 12 and 10 bursts/min to 44 and 55 bursts/min at T2 under sham and active ITD conditions, respectively) and by the presence of multiple burst conglomerates.

At baseline, RRI_{LF} was $1,330 \pm 337$ and $1,673 \pm 367$ ms² for sham and active ITD conditions, respectively ($P = 0.353$). Application of LBNP decreased ($P = 0.002$) these values to 104 ± 41 and 457 ± 137 ms²; there was no difference ($P = 0.372$) in RRI_{LF} values between the two ITD conditions at T2. Similarly, baseline RRI_{HF} values did not differ ($P = 0.591$) between the two ITD conditions (sham: $1,596 \pm 588$ ms²; active: $1,770 \pm 720$ ms²), and LBNP decreased ($P \leq 0.044$) these values (sham: 75 ± 52 ms²; active: 265 ± 106 ms²). Again, there was no difference ($P = 0.557$) in RRI_{HF} between the sham and active ITD trials at T2. TF magnitude decreased ($P < 0.001$) under both conditions during LBNP (sham ITD: 12.6 ± 1.9 to 1.9 ± 0.5 ms/mmHg; active ITD: 13.5 ± 1.7 to 2.5 ± 0.7 ms/mmHg), but there was no difference ($P = 0.92$) between the two ITD conditions at T2.

DISCUSSION

The main findings of this study are that 1) spontaneous breathing through an active ITD protects against hypotension during progressive central hypovolemia by attenuating the reductions in SV and \dot{Q} and 2) there was no evidence of altered systemic sympathetic activation caused by use of the ITD with reduced central blood volume. These findings, in conjunction with previous results from animal studies (33, 35, 43, 41, 52), therefore suggest that the protective effect of the ITD is accomplished primarily by amplifying the natural bellowslike

Table 1. Time domain data at T1 (baseline) and T2 during sham ITD and active ITD trials

Variable	Sham ITD			Active ITD			Sham vs. Active
	T1	T2	<i>P</i> Value (T1 vs. T2)	T1	T2	<i>P</i> Value (T1 vs. T2)	<i>P</i> Value (T2 vs. T2)
RRI, ms	959 \pm 37	550 \pm 65	<0.001	931 \pm 54	480 \pm 24	0.138	0.138
HR, beats/min	64 \pm 2	119 \pm 12	<0.001	67 \pm 4	127 \pm 7	<0.001	0.187
SAP, mmHg	127 \pm 5	72 \pm 7	<0.001	124 \pm 5	102 \pm 3	0.007	<0.001
DAP, mmHg	71 \pm 3	52 \pm 6	<0.001	71 \pm 3	76 \pm 3	0.214	<0.001
MAP, mmHg	92 \pm 4	59 \pm 6	<0.001	91 \pm 4	87 \pm 3	0.423	<0.001
SV, ml	83 \pm 4	30 \pm 3	<0.001	77 \pm 4	35 \pm 2	<0.001	0.005
\dot{Q} , liters	5.3 \pm 0.3	3.5 \pm 0.4	<0.001	5.1 \pm 0.4	4.5 \pm 0.3	0.021	0.002
RR, breaths/min	14 \pm 1	15 \pm 2	0.398	14 \pm 1	11 \pm 1	0.029	0.023

Values are means \pm SE. ITD, impedance threshold device; T2, time point of presyncope during the sham ITD session; RRI, R-to-R interval; HR, heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; SV, stroke volume; \dot{Q} , cardiac output; RR, respiration rate.

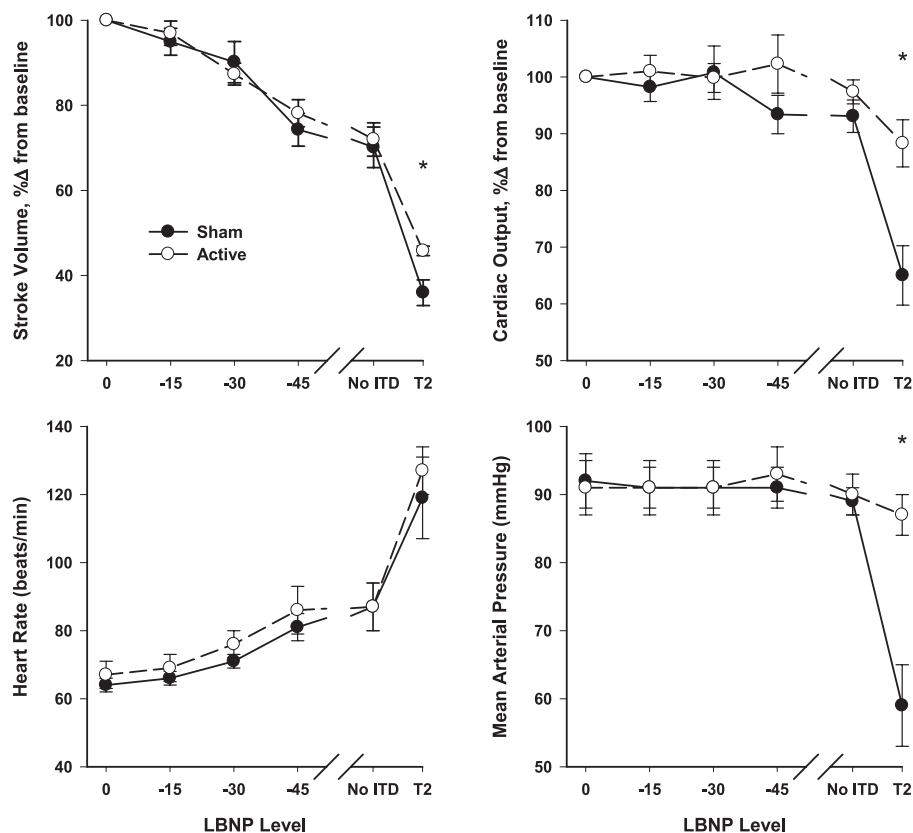


Fig. 1. Hemodynamic variables during the initial stages of lower body negative pressure (LBNP), at the last stage of LBNP before application of a sham or active impedance threshold device ITD (No ITD) and at time point of presyncope during the sham ITD session (T2) during the sham (●, solid lines) and active (○, dashed lines) ITD trials. Absolute levels of heart rate and mean arterial pressure (*bottom*) and percent changes (%Δ) of stroke volume and cardiac output (*top*) did not differ between the two trials at early stages (LBNP levels of 0 to -45 mmHg) or at the last LBNP level at which individuals were not breathing through an ITD (i.e., the “No ITD” point occurred at different LBNP levels for different individuals). Changes in stroke volume and cardiac output as well as absolute mean arterial pressure were altered by breathing through the active ITD. * $P < 0.001$.

function of the thorax to lower intrathoracic pressure during spontaneous inspiration, thereby resulting in an enhancement of venous return.

During both hemorrhage and LBNP, there is a reduction in venous return to the heart, which eventuates in decreases in SV, \dot{Q} , arterial blood pressure, and, ultimately, perfusion to vital organs (17). The ITD was designed to improve venous return by amplifying the vacuum in the thorax during each inspiration, which mechanically draws more blood from the extrathoracic system into the heart (31, 32). In anesthetized pigs following severe hemorrhage, the application of resistance during spontaneous inspiration increased SV, \dot{Q} , and arterial blood pressure (33, 35). Echocardiography in these pigs revealed greater left ventricular end-diastolic volume, suggesting that this increase in SV was due to enhanced ventricular filling (i.e., the Frank-Starling mechanism) (35). In further work in anesthetized pigs, the ITD was shown to increase perfusion pressure to such vital organs as the brain and heart (52), and it was associated with increases in both acute and 24-h survival to severe hemorrhage (43, 51).

The present study extends these results to conscious human subjects taken to the point of cardiovascular collapse by progressive central hypovolemia. ITD breathing attenuated the decreases in SV and \dot{Q} induced by progressive LBNP, resulting in the maintenance of mean arterial pressure and a delay in the onset of cardiovascular collapse (i.e., presyncope). Although we did not measure cardiac dimensions in our subjects, the increase in SV observed is consistent with increased cardiac filling during progressive central hypovolemia. Figure 2 shows temporal correlations between breathing, oscillations in blood pressure and MSNA burst activity under both exper-

imental conditions, as was expected (19). However, breathing against inspiratory resistance may have maintained this relationship by producing a more pronounced temporal entrainment of blood pressure oscillations and MSNA with respiration. These representative data graphically illustrate the action of the active ITD to amplify the normal thoracic pump, as the greater magnitude of oscillations in blood pressure must be the result of greater venous return driven by reduced intrathoracic pressures. Taken together, these results show that inspiratory resistance increases tolerance to central hypovolemia by drawing extrathoracic blood to the heart, thereby protecting SV and \dot{Q} in the face of progressive hypovolemia.

In further support of a primarily mechanical effect of inspiratory resistance to increase ventricular filling, heart rate at T2 did not differ between the two experimental conditions, suggesting that there was no further cardiac sympathetic activation while breathing on the active ITD. Similarly, heart rate was not altered by inspiratory resistance in hemorrhaged pigs (35) or in humans exposed to orthostatic challenges (9, 10). Consistent with this notion, direct recordings of MSNA during breathing through an ITD were unaltered in normovolemic, normotensive subjects (15) and in the one subject in the present investigation for whom there are complete records under both experimental conditions during significant reductions in central blood volume. Furthermore, RRI_{HF} and RRI_{LF} also did not differ between the sham and active ITD trials. Because reductions in RRI_{HF} are correlated with increases in MSNA during progressive LBNP (16), the absence of a different RRI_{HF} response between the sham and active ITD trials suggests an equivalent level of cardiac sympathetic activa-

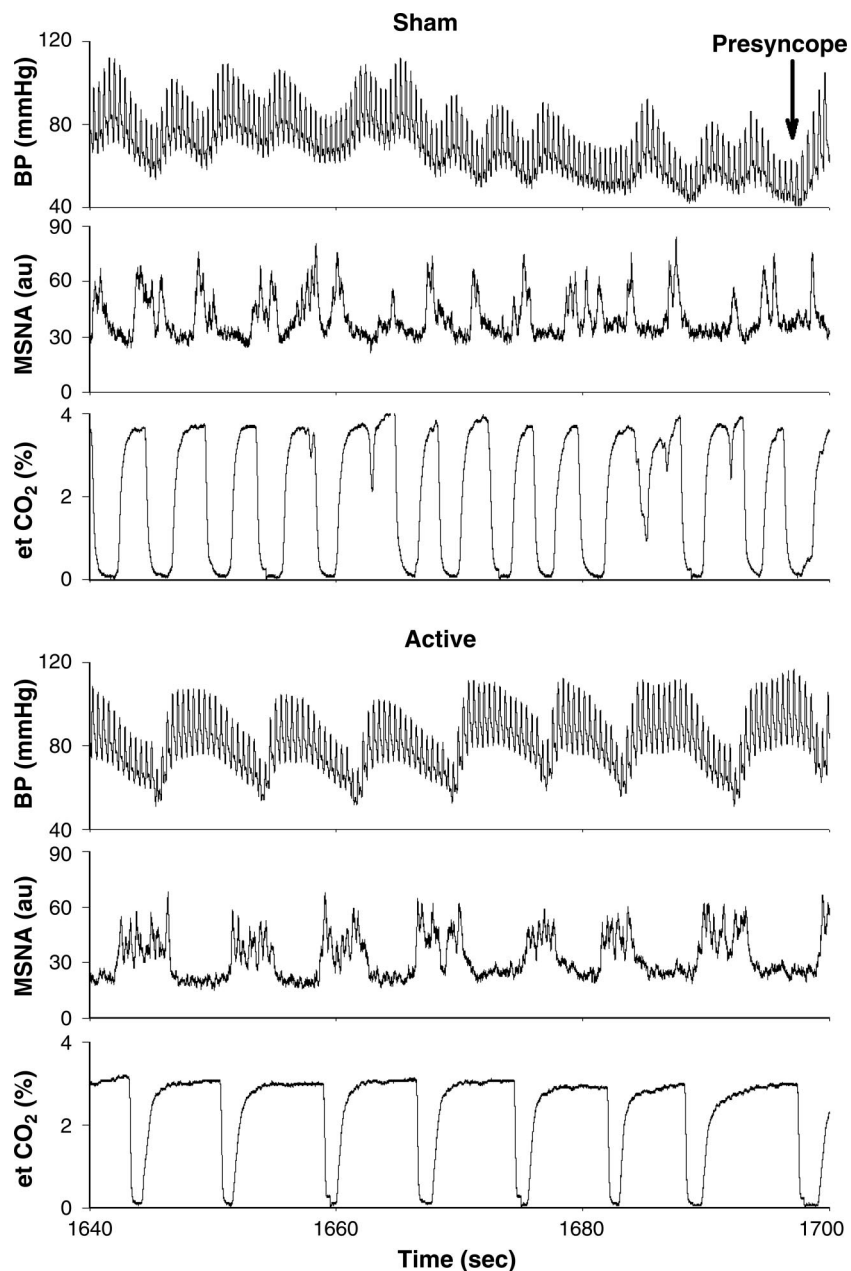


Fig. 2. Blood pressure (BP), muscle sympathetic nerve activity (MSNA), and end-tidal CO₂ (et CO₂) tracings for a single subject under conditions of sham ITD breathing (*top*) and active ITD breathing (*bottom*). au, Arbitrary units.

tion during the two conditions. Finally, breathing on the active ITD did not alter TF at T2, suggesting that baroreflex gain was not different between the two conditions, as has been shown previously in normotensive humans (11, 15). Although not conclusive because of our limited ability to make direct invasive measurements, the absence of change in RRI_{HF} and the TF between systolic blood pressure and RRI are consistent with a relatively minor impact on autonomically mediated reflex responses. These data, however, do not eliminate the possibility of a regional increase in sympathetic activation specific to the splanchnic circulation, which could contribute to the improvement in venous return by moving blood from this high-capacitance reservoir toward the heart (49).

The concept of flow limitation of venous return has been recognized since the early studies of Guyton and colleagues

(22, 23). In these studies using open-chest dogs, venous return at right atrial pressures more negative than -2 to -4 mmHg was limited by collapse of the veins leading into the right atrium; these observations resulted in development of the classic venous return curve depicting this relationship with right atrial pressure (22, 23). Similar venous function curves were subsequently demonstrated in closed-chest preparations (21). Although hemorrhage alone decreased right atrial pressure to approximately -6 mmHg, the use of ITDs set at various levels of inspiratory impedance were able to further decrease right atrial pressure in a "dose-dependent" manner (to < -20 mmHg) in pigs (33, 52), which is well below pressures that should lead to limitations in venous return. Although the present data obtained noninvasively in humans provide no explanation for this paradox, it is clear that inspiratory resistance breathing maintains venous return and SV in both animal

(33, 35, 43, 51, 52) and human (this study; 9, 10) models of central hypovolemia. It is also clear that the beneficial effect of ITD breathing requires a closed chest (unpublished data), indicating that the drop in intrathoracic pressure plays a critical role in improving venous return. In addition to the decrease in intrathoracic and right atrial pressures, ITD breathing may also alter tidal volume and/or end-expiratory lung volume and increases the vigor of respiratory muscle contraction (24); such effects could alter venous return by changing abdominal pressure (44, 45). It is also possible that splanchnic vasoconstriction could mobilize blood from this large reservoir, thereby also contributing to the improvement in venous return (49). Because of the complexity of the pulmonary and circulatory mechanics involved, discrimination of the contributions that each of these factors might play in producing the beneficial effect of ITD breathing on venous return awaits invasive animal studies in which multiple pressure and flow measurements can be made.

The idea that mechanical means might be used to increase venous return during central hypovolemia is not new, as several physical countermeasures have been proposed. For example, the use of medical antishock trousers (MAST) has previously been shown to increase left ventricular end-diastolic volume and \dot{Q} during head-up tilt in humans (48) and hemorrhage in dogs (28). Krediet et al. (26) have also recently demonstrated that the simple maneuver of crossing the legs increases orthostatic tolerance by harnessing the muscle pump to move blood from the legs into the heart during a combined head-up tilt/LBNP protocol. Rather than pumping blood from the periphery to the heart, the ITD accomplishes the same end point (i.e., an increase in venous return) by mechanically amplifying the normal respiratory-induced intrathoracic vacuum, thereby siphoning blood to the heart.

Our experiment is not without limitations. Rather than being directly measured, SV was noninvasively estimated by computing aortic flow pulsations from arterial pressure waveforms obtained from infrared photoplethysmography (50). Using this technology, we observed a linear reduction in SV during progressive LBNP similar in relative magnitude to responses previously reported from our laboratory with the application of CO₂ rebreathing (20) and thoracic electrical bioimpedance (4, 5). In fact, in 89 subjects taken to presyncope using LBNP in our laboratory, simultaneous measurement of SV by Finometer and thoracic electrical bioimpedance yields decreases of 53 ± 2 and $60 \pm 4\%$, respectively ($P = 0.114$; unpublished observations). More importantly, the SV response in our subjects was reproduced during both LBNP exposures before placement of the sham or active ITD (Fig. 1). It is also possible that increases in afterload (as produced by the ITD) could influence pulse contour-derived SV estimates once ITD breathing commenced; recent data, however, suggest that this may not be the case, as SV measured either by pulse contour analysis or by direct measurement using an aortic flow probe was not affected by phenylephrine-induced increases in afterload in anesthetized pigs (27). Thus, although not quantitative in absolute terms, our data suggest that the relative difference in SV obtained from Finometer arterial pressure waveforms represents a valid estimate of the active ITD effect on SV. Another potential limitation of this study was the inability to maintain direct MSNA recordings throughout LBNP in all but one of our subjects. To obviate this, we used spectral analysis of heart

period variability. While it is clear that RRI_{HF} oscillations reflect vagal cardiac control (38), the meaning of the RRI_{LF} oscillations remains controversial (47). Although RRI_{LF} oscillations are associated in some way with fluctuation of both parasympathetic and sympathetic traffic (34, 37), the association with sympathetic traffic is imperfect because RRI_{LF} does not reliably track MSNA during LBNP (16). Recently, however, our laboratory observed a strong inverse relationship between MSNA and RRI_{HF} during LBNP, suggesting that RRI_{HF} tracks parasympathetic withdrawal and simultaneous sympathetic activation appropriately during progressive reductions in central blood volume (16). Because both RRI_{LF} and RRI_{HF} were unaltered at T2, the evidence accrued from both of these indirect indexes of sympathetic activation suggests a lack of systemic autonomic alteration during ITD breathing, although the possibility that sympathetic activation occurs in a specific vascular bed (i.e., splanchnic) cannot be dismissed.

Perspectives (translational physiology). Amplification of a basic physiological phenomenon (i.e., the influence of intrathoracic pressure on venous return) could be useful in a variety of clinical situations in which hypotension is a hallmark of the condition. While our current focus has been on extending the therapeutic window for treatment of traumatic hemorrhage, use of inspiratory resistance might also be useful for such clinical conditions as orthostatic hypotension (36), severe heat stroke or dehydration, severe gastrointestinal bleeding, and septic shock, as well as for patients who develop clinically significant hypotension during renal dialysis or after blood donation (6, 7). It should be noted, however, that breathing on the ITD requires a greater expenditure of respiratory muscle work (by ~ 8 J/min, to a total of 12–16 J/min) (24). Although breathing on the ITD is well tolerated in healthy human subjects, it is unknown whether this increased workload might worsen acidosis in patients already in a state of shock (1, 40). While the increased survival of hemorrhaged pigs suggests that, on balance, ITD breathing is beneficial (43, 51), human clinical trials are needed to settle this issue.

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