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RESEARCH ARTICLE

Effects of inspiratory impedance on the carotid-cardiac baroreflex response in humans

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Abstract We were interested in a therapeutic device designed to increase carotid-cardiac baroreflex sensitivity (BRS) since high BRS is associated with a lower risk for development of hypotension in humans with experimentally-induced central hypovolemia. We hypothesized that spontaneous breathing through an impedance threshold device (ITD) designed to increase negative intrathoracic pressure during inspiration and elevate arterial blood pressure would acutely increase BRS in humans. We tested this hypothesis by measuring heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressures, and carotid-cardiac BRS in 10 female and 10 male subjects breathing through a face mask at three separate ITD conditions: (a) 6 cm H_2O; (b) 12 cm H_2O; and (c) a control (0 cm H_2O). HR was increased ($P = 0.013$) from 64 ± 3 bpm during control to 68 ± 3 bpm at 6 cm H_2O ITD and 71 ± 4 bpm at 12 cm H_2O ITD breathing conditions. During ITD breathing, BRS was not altered but responses were shifted to higher arterial pressures. However, SBP and DBP were elevated for both the 6 and 12 cm H_2O conditions compared to the 0 cm H_2O condition, but returned to control (sham) levels by 30 minutes after cessation of ITD breathing. There were no gender effects for BRS or any hemodynamic responses to breathing through the ITD. We conclude that breathing with inspiratory impedance at relatively low pressures can increase baseline arterial blood pressure, i. e., reset the operational point for SBP on the baroreflex stimulus-response relationship, in healthy subjects. This resetting of the cardiac baroreflex may represent a mechanism that allows blood pressure to increase without a reflex-mediated reduction in HR.

Key words heart rate · blood pressure · baroreflex function · baroreceptor resetting · respiratory resistance

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Introduction

The carotid-cardiac baroreflex contributes to blood pressure regulation during hypovolemic hypotension by reducing vagal activity to the heart and subsequently increasing heart rate and cardiac output. The importance of this reflex is underscored by the association of attenuated tachycardia with the development of severe hypotension under conditions of sinoaortic denervation [12]. Data reported from several investigations on human subjects provide compelling evidence that a greater sensitivity of the carotid-cardiac baroreflex is associated with a lower risk for development of hypotension in humans with experimentally-induced central hypovolemia [4–7, 10, 17–19, 22]. Thus, a therapeutic device designed to increase carotid-cardiac baroreflex sensitivity (BRS) might provide protection against clinical hypotension.

An impedance threshold device (ITD) comprised of a small disposable plastic valve attached to a standard clinical facemask has been developed for application to patients undergoing cardiopulmonary resuscitation [25]. In spontaneously breathing human and animal subjects, the ITD causes resistance during inspiration that creates acute reduction of intrathoracic pressure, elevation of arterial blood pressure, and increased blood flow to vital organs [23–28]. Alterations in intrathoracic and arterial pressures could stimulate low- and high-pressure baroreceptors and subsequently enhance cardiac reflex responses that contribute to the control of cardiac output [2, 3, 8, 9, 15, 16, 29]. If breathing through the ITD increases BRS, the ITD may represent a method of protection against development of hypotension and cardiovascular collapse (e. g., presyncope, circulatory shock) under conditions of central hypovolemia (e. g., orthostatic stress, hemorrhage). The purpose of this investigation was to test the hypothesis that breathing with inspiratory impedance would acutely increase the sensitivity of the vagally-mediated carotid-cardiac baroreflex. Our results suggest that increased heart rate despite elevated arterial blood pressure during spontaneous breathing on an ITD was associated with baroreflex resetting to a higher blood pressure operating point rather than increased reflex sensitivity.

Methods

Subjects

Twenty healthy, normotensive, non-smoking men (N = 10) and women (N = 10) served as subjects. Demographic data for the subjects are presented in Table 1. The subjects had not undergone any particular type of exercise training. Because of the potential effects on baroreflex function, subjects refrained from exercise and stimulants such as caffeine and other non-prescription drugs 48 hours prior to testing. During an orientation period that preceded each experiment, all subjects were made familiar with the laboratory, the protocol, and procedures. Experimental procedures and protocols were reviewed and approved by the Research Council and Human Use Committee of the US Army Institute of Surgical Research and the Human Investigative Review Board of the Kennedy Space Center. Each subject gave written informed voluntary consent to participate in the experiments.

Table 1 Subject group descriptive data

	Females (N = 10)	Males (N = 10)
Age, yr	32 ± 4	33 ± 4
Height, cm	167 ± 2	177 ± 1
Weight, kg	63.8 ± 2.5	78.8 ± 2.9
Heart Rate, bpm	66 ± 3	61 ± 3
Systolic Blood Pressure, mmHg	110 ± 3	120 ± 3
Diastolic Blood Pressure, mmHg	71 ± 2	75 ± 3

Values are mean ± 1 standard error

Protocol

Each subject completed three testing sessions that entailed measurements of arterial blood pressures, heart rate, respiration, and the stimulus-response relationship of the carotid-cardiac baroreflex: (a) during breathing through a face mask with an ITD set at approximately 6 cm H_2O; (b) during breathing through the same face mask with an ITD set at 12 cm H_2O; and, (c) during a control session (breathing through the same face mask with a sham ITD). The order of treatment was randomized and counterbalanced so that one-third of the subjects underwent hemodynamic, respiratory and baroreflex testing during active ITD (6 cm H_2O) treatment first, one-third of the subjects underwent testing during active ITD (12 cm H_2O) treatment first, and one-third of the subjects underwent testing with the sham ITD treatment (control condition) first. An average of approximately one week (mean ± SE = 7.2 ± 0.3 days) intervened between each of the experimental test sessions. All three testing sessions were initiated at the same time of day for any particular subject.

The carotid-cardiac baroreflex stimulus-response relationship, heart rate, arterial blood pressures, and tidal volumes were measured as subjects breathed through a face mask with an ITD. The carotid-cardiac baroreflex stimulus-response relationship, heart rate and arterial blood pressure measurements were repeated at 30 min after completion of the 14-min ITD breathing cycle. This protocol represented a complete experimental session. Valves set at 6 to 12 cm H_2O cracking pressures (i. e., pressures at which the valve opened, allowing air inflow) were chosen because impedance levels as high as 20 cm H_2O were previously proven tolerable and to increase arterial blood pressure in human subjects [28]. Each subject had his/her own disposable facemask. During all experiments, continuous beat-by-beat heart rate (HR) was measured with computer software from an electrocardiogram (ECG) and systolic (SBP) and diastolic (DBP) blood pressures were measured noninvasively by a sphygmomanometric blood pressure monitoring device. Each experimental session was conducted over a period of less than 60 min.

Breathing with the ITD

At the beginning of each experimental testing session, each subject breathed spontaneously through an ITD for 14 min while in the supine position. The ITD is comprised of a 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 (Fig. 1). The ITD was designed to create inspiratory resistance and a small vacuum within the chest of a spontaneously breathing subject. The ITD was attached to a facemask to ensure that a seal between the valve and the skin of the subjects' face was sufficient to eliminate any air leakage (Fig. 2A). During inspiration, blood is drawn from the extrathoracic venous system into the heart each time the subject takes a breath, thereby enhancing cardiac preload [25, 27]. Therefore, use of the ITD results in an immediate increase in arterial blood pressure [23–28, 32]. There is little resistance during exhalation.

Measurement of ventilatory response to ITD breathing

After the initial 3 min of ITD breathing, minute ventilation volume (liters/min) was measured from the additive inspiratory flow for 1 min with an Interface Associates (model VMM 402, Laguna Niguel, CA) turbine transducer (Fig. 2B). Inspiratory impedance was measured during the same time interval using an MKS (model PDR-C-1C, Andover, MA) pressure transducer between the ITD/patient mask interface (Fig. 2B). The analog waveform was recorded on a Gould (Eastlake, OH) strip chart recorder and the change in pressure (negative intrathoracic pressure) was measured in cm H_2O. Respiratory rate was measured by counting the negative pressure deflections occurring on the strip chart during the one-minute time period.

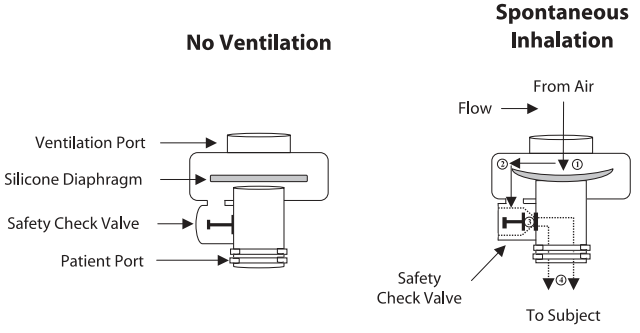

Fig. 1 Drawing illustration of the Impedance Threshold Valve. During spontaneous inspiration, air flow from the ventilation port to the subject causes the silicone diaphragm to close (Step #1). The air flow bypasses the diaphragm to the Safety Check Valve (Step #2). When intrathoracic pressure reaches and exceeds the impedance threshold of the valve, the Safety Check Valve opens (Step #3) and air reaches the subject (Step #4)

Measurement of carotid-cardiac baroreflex

Carotid baroreceptor-cardiac reflex responses were measured in the supine posture with an experimental method described previously [21]. Briefly, a stepping-motor driven bellows was used to deliver a series of pressure and suction steps to a Silastic neck chamber. During held expiration, a pressure of approximately 40 mmHg was delivered to the chamber and held for 5 R-waves; then, with each subsequent R-wave, the pressure was sequentially stepped to about 25, 10, –5, –20, –35, –50, and –65 mmHg, and then returned to ambient pressure (Fig. 3). In this way, the duration of the entire pressure stimulus sequence was 12 to 15 s. During each test session, the stimulus sequence was repeated 5 times and data were averaged for each subject. Previous studies in our laboratory indicated that baroreceptor stimulus-sinus node response relationships measured in this way are highly reproducible [14]. SBP was measured with a sphygmomanometer only once prior to the application of the 5-stimulus sequence trials since changes in reflex arterial pressures are small relative to neck pressure changes [14]. R-R intervals for each pressure step were plotted against estimated carotid distending pressures (CDP = systolic pressure minus neck chamber pressure applied during the heart beat). From the average of each 5-trial sequence of responses, the entire sigmoidal reflex curve could be defined by the 8 pressure steps performed on each subject. The stimulus-response baroreflex relationships were reduced to maximum slope (determined by application of least squares linear regression analysis to every set of three consecutive points on the stimulus-response relationship), and relative position of the operational point (determined from the calculation [(R-R intervals at 0 mmHg neck pressure – minimum R-R intervals)/(maximum R-R interval – minimum R-R intervals)] X 100 %). The maximum slope provided an index of reflex sensitivity and the operational point provided a measure of the relative baroreflex buffering capacity for pressures above and below resting levels.

Statistical analysis

The statistical analysis was a standard 2 group (male, female) by 3 treatments (6 cm H_2O ITD, 12 cm H_2O ITD, control) mixed model analysis of variance. The model was mixed in the sense that subjects were nested within gender groups and crossed with treatments and time [i. e., one between subjects factor (gender) and one within sub-

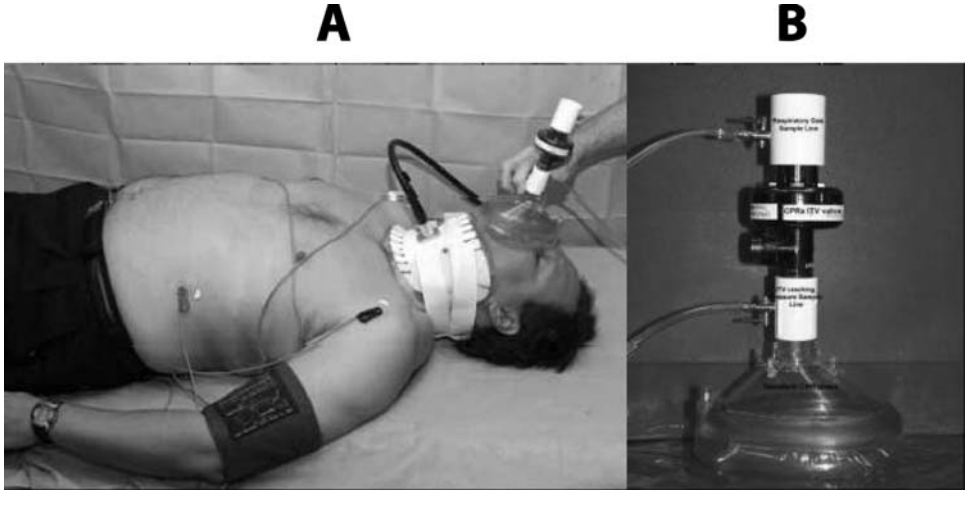

Fig. 2 Photographs of a subject and the experimental setup. **A** illustrates placement of the ITD and neck pressure chamber on a subject instrumented for measurements of heart rate (ECG), blood pressure (BP cuff), and baroreflex sensitivity. **B** illustrates the valve connected to a facemask and sensors for measurement of ventilatory volume/rate and inspiratory pressure

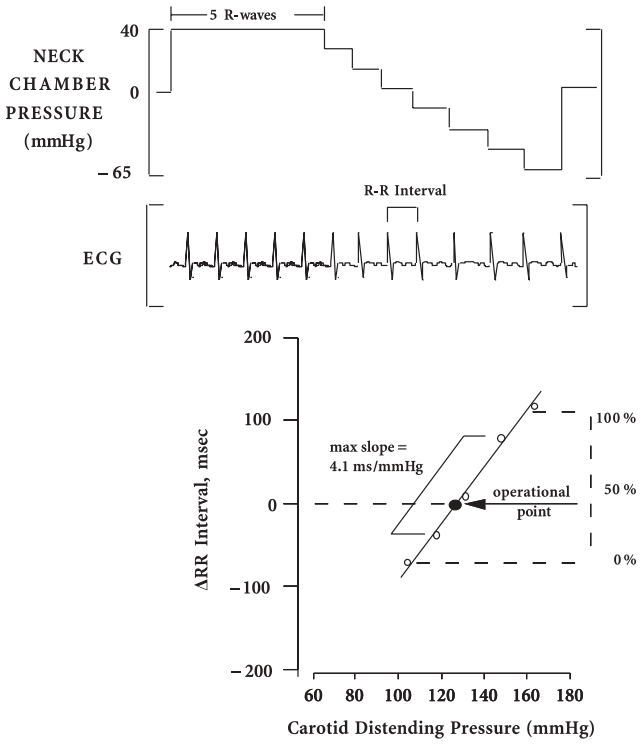

Fig. 3 Sample illustration of stimulus (neck pressure) profile and ECG recording for calculation of the carotid-cardiac baroreflex sensitivity (maximal slope) and relative position of the operational point in an individual subject. See text for detailed description

jects factor (treatment)]. To simplify the statistical analysis and make it more interpretable, separate statistical models were constructed for measurements taken during ITD breathing and 30 min after the cessation of ITD breathing. All main effects and subsequent interactions were analyzed across five dependent effects (HR, SBP, DBP, carotid-cardiac BRS, and baroreflex operational point). Exact P values were calculated for each independent effect and reflect the probability of obtaining the observed or greater effect given only random departure from the assumption of no effects. Orthogonal polynomials (i. e., dose response modeling) or independent contrasts were constructed in the event of statistical differences associated with the main effect of the treatment (i. e., inspiratory impedance level). Standard errors presented in the tables and text and depicted in the figures are raw measures of variation about the specific treatment group mean.

Results

Demographic data

Average and standard error baseline values for age, height, weight, HR, and blood pressures for females and males are presented in Table 1. Male and female groups were matched for age ($F = 0.043$, $P = 0.839$). Subjects showed the expected and well-established differences between genders on height, weight, HR, and blood pressure. For HR and blood pressure, all values were within established normal limits.

Respiratory effects of spontaneous breathing on an ITD

Average peak negative pressures of -9.4 ± 0.3 cm H_2O and -14.4 ± 0.4 cm H_2O were generated during spontaneous breathing on the 6 and 12 cm H_2O ITD, respectively. Total minute ventilation volume did not vary statistically by gender, treatment, or by their interaction (F's < 1.70, P's > 0.198). Overall, respiratory volume averaged 6.6 liters/min for all experimental conditions across both genders. A slight gender by treatment interaction was detected for respiratory frequency. Females (11.4 breaths/min) had slightly higher respiratory frequencies than males (8.9 breaths/min) during control (i. e., zero impedance) breathing with no differences seen during 6 and 12 cm H_2O ITD ($F_{interaction}[2,36] = 3.92$, $P = 0.029$).

Hemodynamic effects of spontaneous breathing on an ITD

Heart rate and arterial blood pressure data during spontaneous breathing through the ITD and 30 min after the cessation of each ITD condition are presented in Table 2. Heart rate increased in a linear fashion with increased resistance during ITD breathing ($F_{linear}[1,36] = 9.48$, $P = 0.004$) but returned to control (sham) levels 30 minutes after cessation of ITD breathing with no observed

Table 2 Heart rate, blood pressure and baroreflex data

	ITD Breathing			30 min Recovery		
	0 cm H_2O	6 cm H_2O	12 cm H_2O	0 cm H_2O	6 cm H_2O	12 cm H_2O
Heart Rate, bpm	63±3	68±3	71±4	61±2	60±3	61±3
SBP, mmHg	115±3	122±4	121±3	114±3	114±3	115±4
DBP, mmHg	73±2	74±2	77±3	73±2	72±2	72±2
BRS, ms/mmHg	4.3±0.8	3.8±0.7	4.5±0.6	4.3±0.9	4.0±0.7	4.5±0.7
Operational Point, %	33±5	38±6	35±4	38±6	36±6	41±7

Values are mean ± 1 standard error. *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *BRS* baroreflex sensitivity

residual effect of the treatment ($F[2,36] = 0.29$, $P = 0.754$). SBP was elevated during ITD breathing for both the 6 and 12 cm H_2O conditions compared to the 0 cm H_2O condition ($F_{0\,vs\,6\,\&\,12}[1,36] = 13.4, P = 0.001$) and returned to control levels during the 30 minute recovery with no continuing effects of the ITD conditions ($F[2,36] = 0.21, P = 0.812$). DBP showed a linear elevation (i. e., response across impedance levels increased in a linear fashion) with increasing ITD resistance ($F_{linear}[1,36] = 4.76$, $P = 0.036$) and returned to control (sham) levels 30 minutes after cessation of ITD breathing ($F[2,36] = 0.61, P = 0.547$).

ITD breathing and gender effects

Total ventilation volume ($F = 0.305, P = 0.583$) and respiratory frequency ($F = 0.583$, $P = 0.448$) during spontaneous breathing on the ITD were not affected by gender. Likewise, gender did not influence the responses of SBP ($F = 0.135$, $P = 0.874$), DBP ($F = 0.275$, $P = 0.761$), HR ($F = 0.460$, $P = 0.635$), carotid-cardiac BRS ($F = 1.848$, $P = 0.172$), or carotid-cardiac baroreflex operational point ($F = 0.579$, $P = 0.566$) across treatment during spontaneous breathing through the ITD.

Carotid-cardiac baroreflex

Fig. 4 demonstrates the mean (± SE) carotid baroreceptor stimulus-cardiac response relationships for ITD treatment by time for all 20 subjects. From a total of 8 pressure stimuli, the points for each time and condition plotted in Fig. 4 represent the 5 pressure stimuli that produced the most linear portion (slope) of the sigmoidal stimulus-response relationship. Sensitivity and position of the operational point for the carotid-cardiac baroreflex during spontaneous breathing through the ITD and 30 min after the cessation of each ITD condition are presented in Table 2. No treatment effects were seen across ITD breathing or recovery for baroreflex sensitivity or the relative position (%) of the operational point on the stimulus-response relationship (F's$[2,36] \leq 1.40, P$'s ≥ 0.260). Because the curves were parallel (i. e., no change in slope), the magnitude of the shift in the baroreflex stimulus-response relationship (i. e., resetting) was quantified by calculating the average change in SBP across the linear portion of the curve for each subject. This analysis revealed that the baroreflex stimulus-response relationship underwent a shift of $+7 \pm 2$ and $+6 \pm 2$ mmHg ($F = 3.291$, $P = 0.003$) during spontaneous breathing through the ITD at 6 and 12 cm H_2O compared to the control (sham) treatment (Fig. 4).

Discussion

Arterial and/or cardiopulmonary baroreceptor stimulation by periodic alterations in intrathoracic or arterial blood pressure may provide a stimulus for an acute change in the sensitivity of the carotid-cardiac baroreflex response [2, 3, 8, 9, 15, 16, 29]. We therefore hypoth-

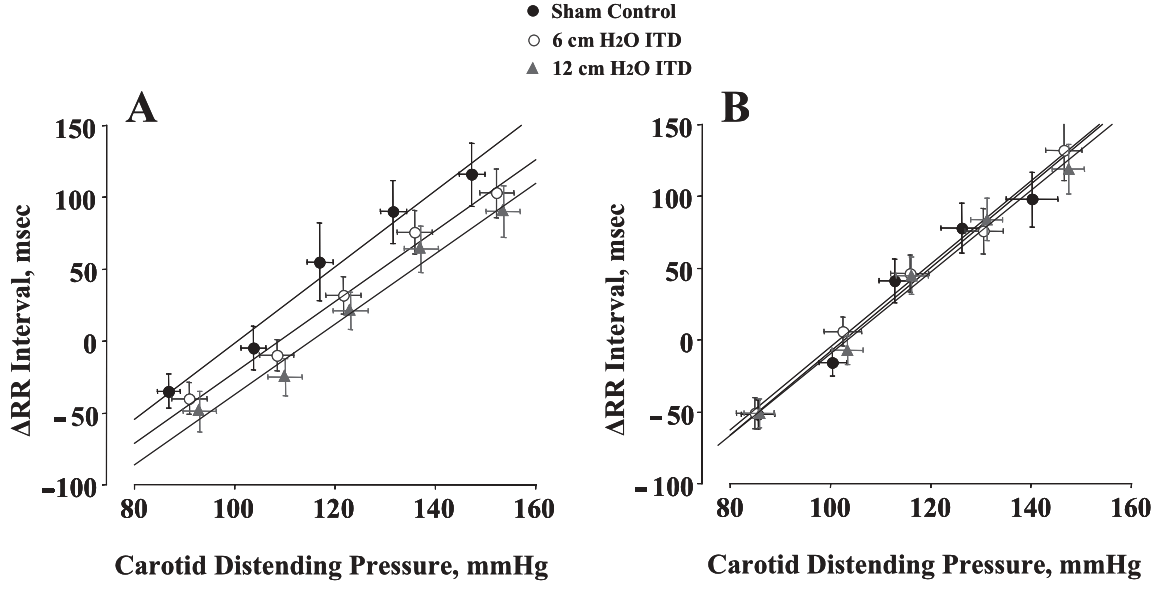

Fig. 4 Baroreflex stimulus-response relationships between estimated carotid distending pressure and change (Δ) in R-R interval during (**A**) and 30 min after (**B**) spontaneous breathing on the ITD at 0 cm H_2O resistance (sham control, closed circles), 6 cm H_2O resistance (open circles), and 12 cm H_2O resistance (closed triangles). Linear regressions are calculated from mean carotid distending pressure and ΔR-R interval values of 20 subjects. Symbols and bars represent mean ± 1 standard error

esized that the use of respiratory resistance (i. e., spontaneous breathing through an ITD) designed to reduce intrathoracic pressure and elevate arterial blood pressures would acutely increase the sensitivity of the carotid-cardiac baroreflex. Our data confirmed that application of the ITD acutely decreased intrathoracic pressure and increased SBP similar to previously reported observations [23–28, 32]. Against expectations, we found no alteration in baroreflex sensitivity during the ITD conditions compared with the control condition. However, a major new finding of the present investigation was that the stimulus-response relationship of the carotid-cardiac baroreflex demonstrated a significant shift, suggesting an acute resetting to a higher operational range of blood pressure for the control of heart rate. The findings are also consistent with the hypothesis that an increase in central blood volume during inspiration through inspiratory impedance contributed to or caused the acute resetting of the carotid-cardiac baroreflex.

Acute increases in cardiac baroreflex sensitivity have been associated with greater elevations in arterial blood pressure. For example, an average increase of 43 % in cardiac baroreflex sensitivity was observed following repeated respiratory straining maneuvers that increased average SBP by approximately 24 mmHg [8]. Cardiac baroreflex sensitivity was also increased by approximately 20 % when lower body positive pressure was used to increase systolic blood pressure from 117 ± 2 mmHg to 131 ± 5 mmHg (Δ = +14 mmHg) [14, 15]. Likewise, elevation of mean arterial blood pressure from 119 ± 4 mmHg to 139 ± 3 mmHg (Δ = +20 mmHg) induced by acute anti-G suit application increased carotid baroreflex sensitivity by 59 % when applied under orthostatic conditions [9]. We observed no increase in baroreflex sensitivity associated with the acute elevation in arterial blood pressure induced by spontaneous breathing in the present investigation. Since the average elevation in SBP was only 6 to 7 mmHg in the present study, it is possible that we failed to observe any change in baroreflex sensitivity because the magnitude of arterial baroreceptor loading failed to reach a minimum stimulus threshold. This notion is consistent with previous observations that increased carotid baroreceptor afferent nerve firing in response to graded elevations in pulsatile pressure was elicited only after the pressure stimulus reached a minimal level [2, 3].

The resetting of the carotid-cardiac baroreflex by spontaneous breathing on an ITD was characterized by a shift of the stimulus-response relationship to a higher blood pressure operating range without a change in baroreflex sensitivity (Fig. 3 A) or relative position of the operational point (i. e., baseline HR/SBP relationship). The return of the carotid-cardiac baroreflex stimulus-response relationship to an identical blood pressure operating range by 30 min after the cessation of all three ITD experimental conditions (Fig. 3 B) is consistent with the reproducibility of the baroreflex [14] and indicates that the acute resetting was a real phenomenon. The magnitude of resetting in our subjects (ΔSBP = +7 mmHg) is about one-third of that associated with acute phenylephrine infusion (+ 22 mmHg; [20]) and chronic hypertension (+26 mmHg; [13]) reported by previous investigators who used neck suction/pressure methods of baroreflex measurement in humans similar to those used in the present study. Although modest, the magnitude of the carotid-cardiac baroreflex resetting observed in our experiment may be important in that it occurred in healthy normovolemic, normotensive subjects in the supine position, which optimizes venous return. Our intention in the present investigation was to demonstrate tolerance and efficacy of elevating blood pressure in a 'normal' physiological state before exposing human subjects to conditions of central hypovolemia. The possibility that resetting of the carotid-cardiac baroreflex may be of greater magnitude and contribute significantly to maintenance or elevation in heart rate and arterial blood pressure induced by spontaneous resistance breathing during hemorrhage or orthostatic challenges may be better demonstrated with application of the ITD in human subjects exposed to models of central hypovolemia.

In addition to the shift of the baroreflex stimulus-response relationship to a higher blood pressure operating range, the elevation in HR during spontaneous breathing on the ITD was a unique and unexpected finding in the present study. Since arterial blood pressure was increased with inspiratory resistance, we anticipated a bradycardic response mediated by arterial baroreflex feedback control. In contrast, ITD breathing elicited a tachycardic response in the face of rising arterial blood pressure. Although this tachycardic response seems contraindicated, it is similar to the concurrent elevation in HR and arterial blood pressure responses observed during physical exercise. Two additional similarities that exist in the comparison of the HR-blood pressure responses reported during exercise and those observed in the present investigation is increased negative intrathoracic pressures [30] and resetting of the cardiac baroreflex stimulus-response relationship to a higher operating range [29].

Although the mechanism(s) is unknown, we cannot dismiss the possibility that elevated HR during spontaneous breathing on an ITD could simply reflect an "exercise" effect from the increased work of breathing against resistance. If this hypothesis were true, we would expect withdrawal of vagal activity and no significant change in sympathetic activity with heart rate below 100 bpm during physical exercise [31]. To test this hypothesis, we have initiated subsequent experiments in an attempt to understand the mechanism(s) involved in the tachycardic response to ITD. Contrary to the notion that

the elevation of HR during use of an ITD represents a response to exercise, our preliminary data demonstrate no change in cardiac vagal activity (as indicated by no effect on the standard deviation of R-R interval) and a clear attenuation (~30 %) in muscle sympathetic nerve activity (Fig. 5). These preliminary observations suggest that the elevation in HR is initiated by a mechanical rather than metabolic stimulus, and therefore may not represent an "exercise" effect *per se*. Rather, a larger negative intrathoracic pressure resulting from inspiratory resistance may mechanically initiate a chronotropic response as a result of enhanced cardiac filling (e. g., the Bainbridge reflex, stretch of the SA node).

Spontaneous breathing through an ITD has been shown to cause an immediate increase in arterial blood pressure when applied in different clinical models associated with significant life-threatening hypotension such as hemorrhage [23–28]. The concept by which the ITD functions to increase blood pressure is based on the mechanics of producing a vacuum within the thorax during each inspiration, and subsequently increasing venous return (preload) to the heart [25–27]. The results of the present investigation reveal an additional mechanism by which the ITD may function to protect arterial blood pressure during conditions of central hypovolemia. The resetting of the carotid-cardiac baroreflex to a higher arterial pressure operating range would allow blood pressure to be elevated without reflex inhibition of HR. Subsequently, in addition to enhanced cardiac filling and stroke volume during central hypovolemia, a sustained tachycardia caused by ITD application would act to maximize the increase in cardiac output. The lack of effect on vagal baroreflex sensitivity does not preclude the possibilities that the ITD could be elevating HR by inhibiting parasympathetic tonic activity, stimulating sympathetic activity, or inducing mechanical stimulation. However, the absence of change in R-R interval standard deviation and attenuated muscle sympathetic nerve activity (Fig. 5) during spontaneous breathing on the ITD in our preliminary experiments provide support to the latter hypothesis.

Previous investigations have revealed differences in baroreflex functions between males and females [1, 5, 11]. Because our subject population was composed of 50 % males and 50 % females, we had the opportunity to examine the influence of gender on the hemodynamic and baroreflex responses to inspiratory resistance. Like previous studies, we observed that our female subjects had higher average HR and lower blood pressures and baroreflex sensitivity than their male counterparts (although differences in HR and baroreflex sensitivity were not statistically distinguishable due to large intergroup variability). More importantly, both male and female subjects in our study demonstrated a similar resetting of the carotid-cardiac baroreflex stimulus-response relationship to a higher blood pressure range in response to elevated SBP and HR induced by increased inspiratory resistance. Therefore, we conclude that application of ITD (i. e., inspiratory resistance) is equally effective in females and males.

Breathing through the ITD was well tolerated by our subjects. Although the difference in ventilatory mechanics (volume and rate) was negligible, the subjects clearly described the additional difficulty (work) required to

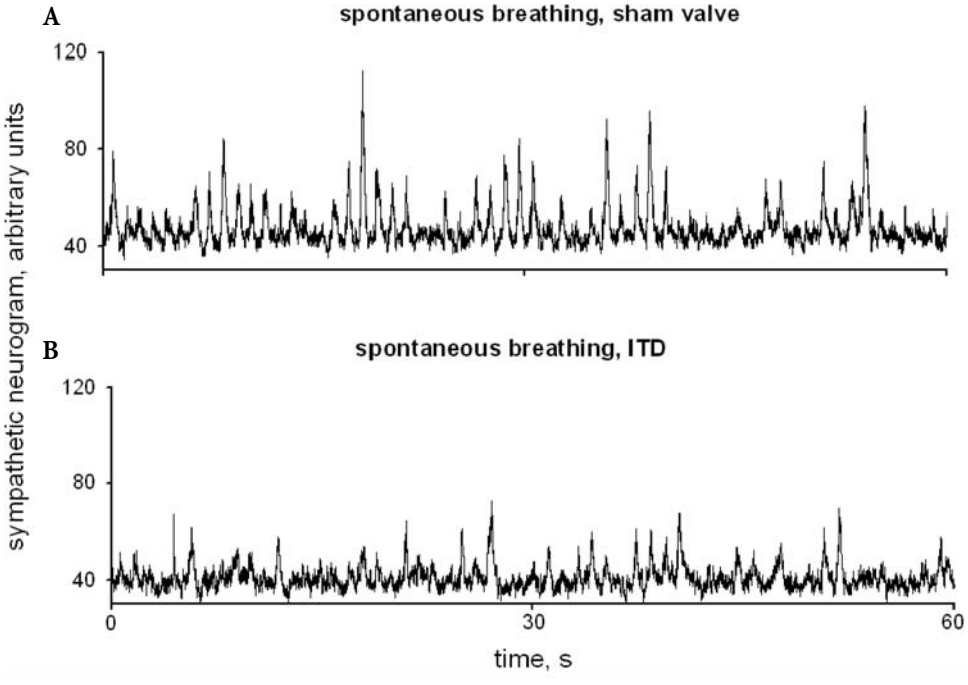

Fig. 5 Recordings of muscle sympathetic nerve activity (MSNA) in a human subject during spontaneous breathing through a sham (**A**) and 6 cm H_2O ITD (**B**). The standard deviation for R-R interval was 37 and 35 ms for sham and 6 cm H_2O ITD. Average MSNA during sham ITD was 23 bursts/min compared to 16 bursts/min in the 6 cm H_2O ITD condition

breathe at the 12 cm H_2O resistance compared with the 6 cm H_2O resistance. In light of the statistically similar effects on carotid-cardiac baroreflex function and elevation in SBP during breathing on the 6 and 12 cm H_2O ITD, our results suggest that a breathing resistance not more than 6 cm H_2O may provide maximum efficiency and comfort for producing optimum elevations in arterial blood pressure.

In summary, we demonstrated that spontaneous breathing through an ITD designed to increase resistance during inspiration shifts the vagally-mediated carotid-cardiac baroreflex stimulus-response relationship to a higher blood pressure operating range, allowing the elevation of HR in the presence of relative increases in arterial pressures. Although unsubstantiated, the tachycardia induced by ITD may function to further protect cardiac output in conditions of acute central hypovolemia. Since attenuated reflex HR responses are associated with cardiovascular collapse during conditions of acute central hypovolemia, the results of this investigation may be relevant to the application of the ITD for the treatment of hemorrhagic shock or orthostatic hypotension.

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Disclaimer: K. Lurie is a co-inventor of the impedance threshold device and founded Advanced Circulatory Systems Inc to develop the device.

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