

Victor A. Convertino  
Duane A. Ratliff  
Kathy L. Ryan  
William H. Cooke  
Donald F. Doerr  
David A. Ludwig  
Gary W. Muniz  
Deanna L. Britton  
Savran D. Clah  
Kathleen B. Fernald  
Alicia F. Ruiz  
Ahamed Idris  
Keith G. Lurie

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

Received: 26 June 2003  
Accepted: 3 March 2004

V. A. Convertino, Ph.D. (✉) · K. L. Ryan ·  
W. H. Cooke  
US Army Institute of Surgical Research  
3400 Rawley E. Chambers Avenue  
Building 3611  
Fort Sam Houston (TX) 78234-6315, USA  
Tel.: +1-210/916-5633  
Fax: +1-210/916-5992  
E-Mail: victor.convertino@amedd.army.mil

D. A. Ratliff  
Bionetics Corporation  
NASA  
Kennedy Space Center (FL), USA

D. F. Doerr  
Biological & Chemical Laboratories Branch  
NASA  
Kennedy Space Center (FL), USA

D. A. Ludwig  
Dept. of Pediatrics  
Georgia Prevention Institute  
Medical College of Georgia  
Augusta (GA), USA

G. W. Muniz  
Professional Performance Development  
Group, Inc.  
San Antonio (TX), USA

D. L. Britton · S. D. Clah · K. B. Fernald ·  
A. F. Ruiz  
Spaceflight and Life Sciences Training  
Program  
NASA  
Kennedy Space Center (FL), USA

A. Idris  
Dept. of Emergency Medicine,  
Anesthesiology & Medicine  
University of Florida  
Gainesville (FL), USA

K. G. Lurie  
Advanced Circulatory Systems, Inc.  
Minneapolis (MN), USA

K. G. Lurie  
Dept. of Emergency Medicine  
University of Minnesota  
Minneapolis (MN), USA

**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<sub>2</sub>O;

(b) 12 cm H<sub>2</sub>O; and (c) a control (0 cm H<sub>2</sub>O). HR was increased ( $P = 0.013$ ) from  $64 \pm 3$  bpm during control to  $68 \pm 3$  bpm at 6 cm H<sub>2</sub>O ITD and  $71 \pm 4$  bpm at 12 cm H<sub>2</sub>O 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<sub>2</sub>O conditions compared to the 0 cm H<sub>2</sub>O 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

| Report Documentation Page                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                   |                                    |                                          | Form Approved<br>OMB No. 0704-0188       |                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|------------------------------------|------------------------------------------|------------------------------------------|---------------------------------|
| Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. |                                   |                                    |                                          |                                          |                                 |
| 1. REPORT DATE<br><b>01 AUG 2004</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                   | 2. REPORT TYPE<br><b>N/A</b>       |                                          | 3. DATES COVERED<br><b>-</b>             |                                 |
| 4. TITLE AND SUBTITLE<br><b>Effects of inspiratory impedance on the carotid-cardiac baroreflex response in humans.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                   |                                    |                                          | 5a. CONTRACT NUMBER                      |                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                   |                                    |                                          | 5b. GRANT NUMBER                         |                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                   |                                    |                                          | 5c. PROGRAM ELEMENT NUMBER               |                                 |
| 6. AUTHOR(S)<br><b>Convertino V. A., Ratliff D. A., Ryan K. L., Doerr D. F., Ludwig D. A., Muniz G. W., Britton D. L., Klah S. D., Fernald K. B., Ruiz A. F., Idris A., Lurie K. G.,</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                   |                                    |                                          | 5d. PROJECT NUMBER                       |                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                   |                                    |                                          | 5e. TASK NUMBER                          |                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                   |                                    |                                          | 5f. WORK UNIT NUMBER                     |                                 |
| 7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)<br><b>United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX 78234</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                   |                                    |                                          | 8. PERFORMING ORGANIZATION REPORT NUMBER |                                 |
| 9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                   |                                    |                                          | 10. SPONSOR/MONITOR'S ACRONYM(S)         |                                 |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                   |                                    |                                          | 11. SPONSOR/MONITOR'S REPORT NUMBER(S)   |                                 |
| 12. DISTRIBUTION/AVAILABILITY STATEMENT<br><b>Approved for public release, distribution unlimited</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                   |                                    |                                          |                                          |                                 |
| 13. SUPPLEMENTARY NOTES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                   |                                    |                                          |                                          |                                 |
| 14. ABSTRACT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                   |                                    |                                          |                                          |                                 |
| 15. SUBJECT TERMS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                   |                                    |                                          |                                          |                                 |
| 16. SECURITY CLASSIFICATION OF:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                   |                                    | 17. LIMITATION OF ABSTRACT<br><b>SAR</b> | 18. NUMBER OF PAGES<br><b>11</b>         | 19a. NAME OF RESPONSIBLE PERSON |
| a REPORT<br><b>unclassified</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | b ABSTRACT<br><b>unclassified</b> | c THIS PAGE<br><b>unclassified</b> |                                          |                                          |                                 |

## 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

**Table 1** Subject group descriptive data

|                                | Females<br>(N 10) | Males<br>(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

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.

### 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<sub>2</sub>O; (b) during breathing through the same face mask with an ITD set at 12 cm H<sub>2</sub>O; 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<sub>2</sub>O) treatment first, one-third of the subjects underwent testing during active ITD (12 cm H<sub>2</sub>O) 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<sub>2</sub>O cracking pressures (i.e., pressures at which the valve opened, allowing air inflow) were chosen because impedance levels as high as 20 cm H<sub>2</sub>O 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.

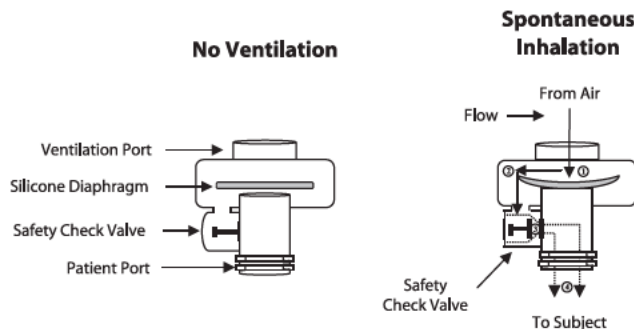
### Breathing with the ITD

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.

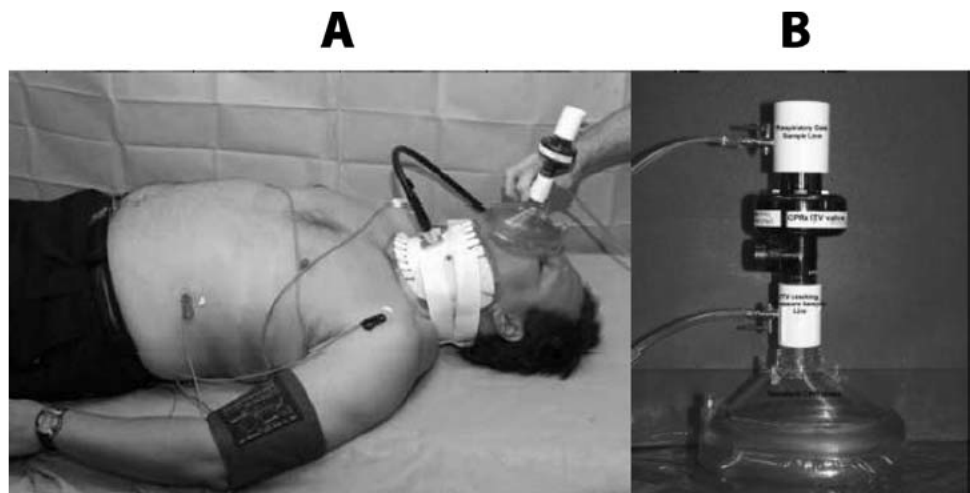
#### ■ Measurement of ventilatory response to ITD breathing

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<sub>2</sub>O. Respiratory



**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)

**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



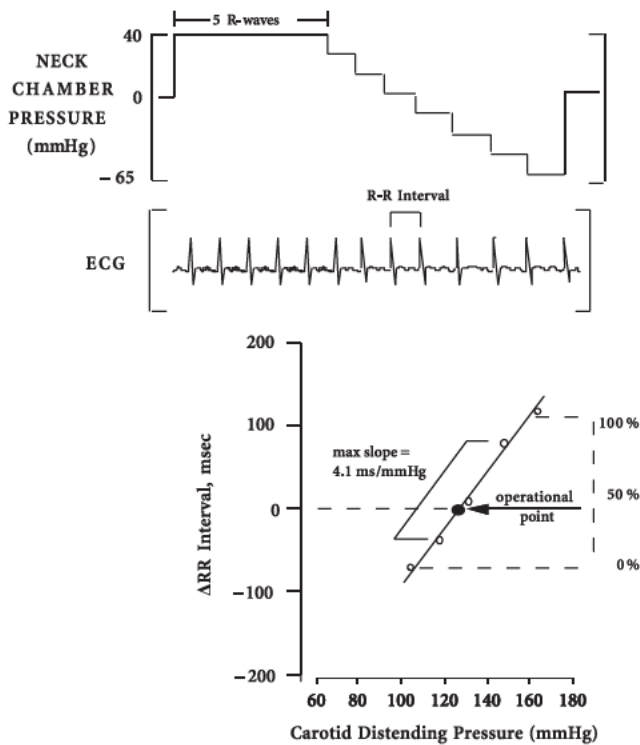
rate was measured by counting the negative pressure deflections occurring on the strip chart during the one-minute time period.

#### ■ 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<sub>2</sub>O ITD, 12 cm H<sub>2</sub>O 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. 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.

**Table 2** Heart rate, blood pressure and baroreflex data

|                      | ITD Breathing         |                       |                        | 30 min Recovery       |                       |                        |
|----------------------|-----------------------|-----------------------|------------------------|-----------------------|-----------------------|------------------------|
|                      | 0 cm H <sub>2</sub> O | 6 cm H <sub>2</sub> O | 12 cm H <sub>2</sub> O | 0 cm H <sub>2</sub> O | 6 cm H <sub>2</sub> O | 12 cm H <sub>2</sub> O |
| 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

## 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  $-9.4 \pm 0.3$  cm H<sub>2</sub>O and  $-14.4 \pm 0.4$  cm H<sub>2</sub>O were generated during spontaneous breathing on the 6 and 12 cm H<sub>2</sub>O 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<sub>2</sub>O ITD ( $F_{\text{interaction}}[2,36] = 3.92$ ,  $P = 0.029$ ).

### 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 ( $F_{\text{linear}}[1,36] = 9.48$ ,  $P = 0.004$ ) but returned to control (sham) levels 30 minutes after cessation of ITD breathing with no observed

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<sub>2</sub>O conditions compared to the 0 cm H<sub>2</sub>O condition ( $F_{0\text{ vs }6\&12}[1,36]=13.4$ ,  $P=0.001$ ) 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 ( $F_{\text{linear}}[1,36]=4.76$ ,  $P=0.036$ ) 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.

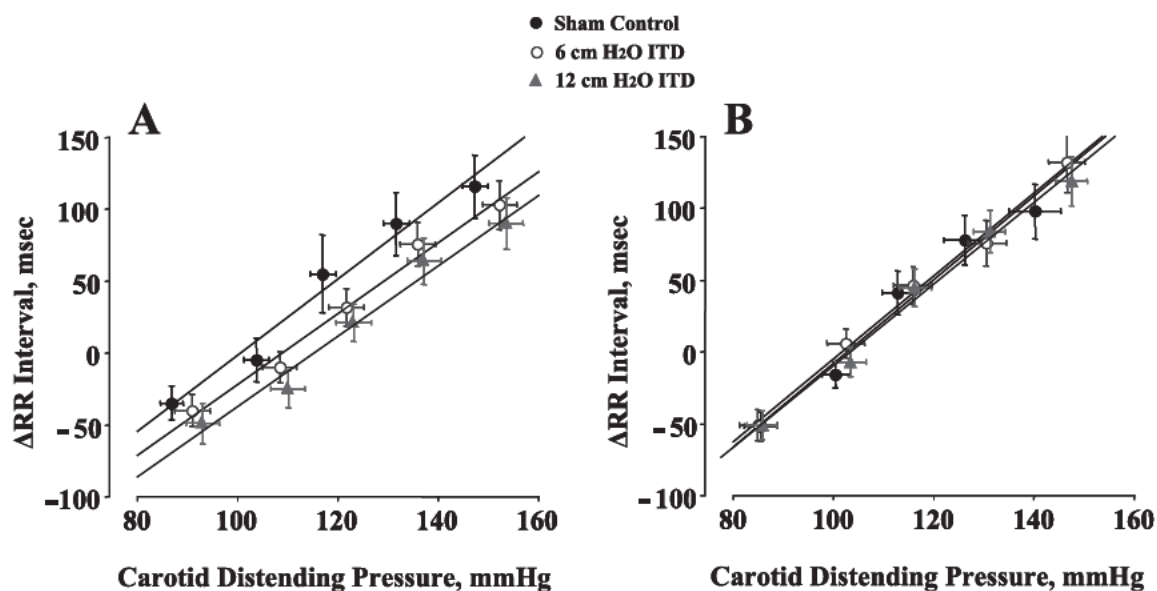
### ■ Carotid-cardiac baroreflex

Fig. 4 demonstrates the mean ( $\pm$  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 ( $F_s[2,36] \leq 1.40$ ,  $P_s \geq 0.260$ ). 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<sub>2</sub>O 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 ( $\Delta$ ) in R-R interval during (A) and 30 min after (B) spontaneous breathing on the ITD at 0 cm H<sub>2</sub>O resistance (sham control, closed circles), 6 cm H<sub>2</sub>O resistance (open circles), and 12 cm H<sub>2</sub>O resistance (closed triangles). Linear regressions are calculated from mean carotid distending pressure and  $\Delta$ R-R interval values of 20 subjects. Symbols and bars represent mean  $\pm$  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  $117 \pm 2$  mmHg to  $131 \pm 5$  mmHg ( $\Delta = +14$  mmHg) [14, 15]. Likewise, elevation of mean arterial blood pressure from  $119 \pm 4$  mmHg to  $139 \pm 3$  mmHg ( $\Delta = +20$  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. 3A) 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. 3B) 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 ( $\Delta$ SBP = +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 ( $\sim 30\%$ ) 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).

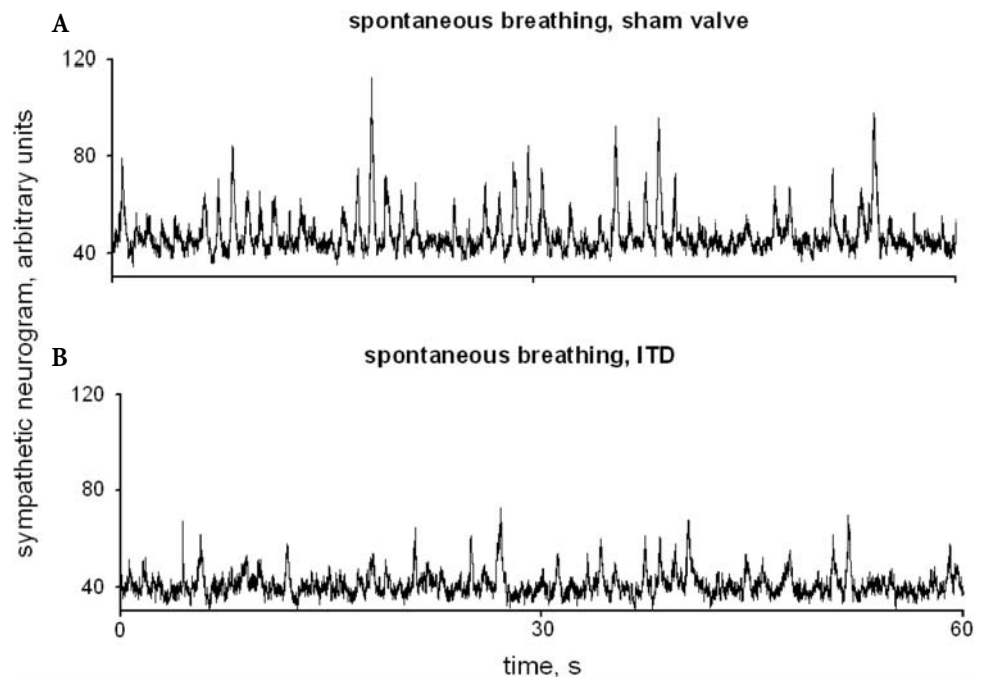
Spontaneous breathing through an ITD has been shown to cause an immediate increase in arterial blood pressure when applied in different clinical models associated with significant life-threatening hypotension such as hemorrhage [23–28]. The concept by which the ITD functions to increase blood pressure 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 out-

put. 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<sub>2</sub>O ITD (B). The standard deviation for R-R interval was 37 and 35 ms for sham and 6 cm H<sub>2</sub>O ITD. Average MSNA during sham ITD was 23 bursts/min compared to 16 bursts/min in the 6 cm H<sub>2</sub>O ITD condition



breathe at the 12 cm H<sub>2</sub>O resistance compared with the 6 cm H<sub>2</sub>O 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<sub>2</sub>O ITD, our results suggest that a breathing resistance not more than 6 cm H<sub>2</sub>O 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.

**Acknowledgements** The authors thank the subjects for their cheerful cooperation; Barry Slack and Robert Cummings for their engineering and technical assistance during the experiments; Cathy DiBiase for her assistance with medical monitoring of the subjects during the experiments; Jacqueline Crissey for assistance with data collection; and the participation of the 2002 NASA Space Life Sciences Training Program for their assistance in data collection and analysis.

This research was supported by a Cooperative Research and Development Agreement between the US Army Institute of Surgical Research and the National Aeronautics and Space Administration (CRDA No. DAMD17-01-0112). The views expressed herein are the views of the authors and are not to be construed as representing those of the National Aeronautics and Space Administration, Department of Defense or Department of the Army.

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

## References

1. Abdel-Rahman AR, Merrill RH, Wooles WR (1994) Gender-related differences in the baroreceptor reflex control of heart rate in normotensive humans. *J Appl Physiol* 77:606–613
2. Chappleau MW, Abboud FM (1987) Contrasting effects of static and pulsatile pressure on carotid baroreceptor activity in dogs. *Circ Res* 61:648–657
3. Chappleau MW, Abboud FM (1989) Determinants of sensitization of carotid baroreceptors by pulsatile pressure in dogs. *Circ Res* 65:566–577
4. Convertino VA (1991) Carotid-cardiac baroreflex: relation with orthostatic hypotension following simulated microgravity and implications for development of countermeasures. *Acta Astronautica* 23:9–17
5. Convertino VA (1998) Gender differences in autonomic functions associated with blood pressure regulation. *Am J Physiol* 275:R1909–R1920
6. Convertino VA, Adams WC, Shea JD, Thompson CA, Hoffler GW (1991) Impairment of the carotid-cardiac vagal baroreflex in wheelchair-dependent quadriplegics. *Am J Physiol Regulatory Integrative Comp Physiol* 260: R576–R580
7. Convertino VA, Doerr DE, Eckberg DL, Fritsch JM, Vernikos-Danellis J (1990) Head-down bedrest impairs vagal baroreflex responses and provokes orthostatic hypotension. *J Appl Physiol* 68:1458–1464
8. Convertino VA, Ratliff DA, Doerr DE, Ludwig DA, Muniz GW, Benedetti E, Charvarria J, Koreen S, Nguyen C, Wang J (2003) Effects of arterial blood pressure loading on cardiac and vasoconstrictive baroreflex responses. *Aviat Space Environ Med* 74:212–219
9. Convertino VA, Reister CA (2000) Effects of G-suit protection on carotid-cardiac baroreflex function. *Aviat Space Environ Med* 71:31–36
10. Convertino VA, Sather TM (2000) Effects of cholinergic and adrenergic blockade on orthostatic tolerance in healthy subjects. *Clin Auton Res* 10: 327–336
11. Convertino VA, Tripp LD, Ludwig DA, Duff J, Chellette TL (1998) Female exposure to high G: chronic adaptations of cardiovascular functions. *Aviat Space Environ Med* 69:875–882
12. Cowley AW Jr, Liard JF, Guyton AC (1973) Role of the baroreceptor reflex in daily control of arterial pressure and other variables in dogs. *Circ Res* 32:564–576
13. Eckberg DL (1979) Carotid baroreflex function in young men with borderline blood pressure elevation. *Circulation* 59:632–636
14. Eckberg DL, Convertino VA, Fritsch JM, Doerr DE (1992) Reproducibility of human vagal carotid baroreceptor-cardiac reflex responses. *Am J Physiol Regul Integr Comp Physiol* 263: R215–R220
15. Eiken O, Convertino VA, Doerr DE, Dudley GA, Morariu G, Mekjavic IB (1991) Interaction of the carotid baroreflex, the muscle chemoreflex and the cardiopulmonary baroreflex in man during exercise. *The Physiologist* 34(Suppl):S118–S120
16. Eiken O, Convertino VA, Doerr DE, Dudley GA, Morariu G, Mekjavic IB (1992) Characteristics of the carotid baroreflex in man during normal and flow-restricted exercise. *Acta Physiol Scand* 144:325–331
17. El-Sayed H, Hainsworth R (1995) Relationship between plasma volume, carotid baroreceptor sensitivity and orthostatic tolerance. *Clin Sci* 88: 463–470
18. Engelke KA, Shea JD, Doerr DE, Convertino VA (1992) Enhanced carotid-cardiac baroreflex response and elimination of orthostatic hypotension 24 hours after acute exercise in paraplegics. *Paraplegia* 30:872–879
19. Engelke KA, Shea JD, Doerr DE, Convertino VA (1994) Autonomic functions and orthostatic responses 24 hours after acute intense exercise in paraplegic subjects. *Am J Physiol Regul Integr Comp Physiol* 266: R1189–R1196
20. Fritsch JM, Rea RF, Eckberg DL (1989) Carotid baroreflex resetting during drug-induced arterial pressure changes in humans. *Am J Physiol Regul Integr Comp Physiol* 256: R549–R553

21. Ludwig DA, Convertino VA (1991) A statistical note on the redundancy of nine standard baroreflex parameters. *Aviat Space Environ Med* 62:172–175
22. Ludwig DA, Convertino VA (1994) Predicting orthostatic intolerance: physics or physiology? *Aviat Space Environ Med* 65:404–411
23. Lurie KG, Coffeen PR, Shultz JJ, McKnite SH, Detloff BS (1995) Improving active compression-decompression cardiopulmonary resuscitation with an inspiratory impedance valve. *Circ* 91: 1629–1632
24. Lurie KG, Mulligan KA, McKnite S, Detloff B, Lindstrom P, Lindner KH (1998) Optimizing standard cardiopulmonary resuscitation with an inspiratory impedance threshold valve. *Chest* 113:1084–1090
25. Lurie KG, Voelckel W, Plaisance P, Zielinski T, McKnite S, Kor D, Sukhum P (2000) Use of an inspiratory impedance threshold valve during cardiopulmonary resuscitation: a progress report. *Resuscitation* 44:219–230
26. Lurie KG, Zielinski T, McKnite S, Sukhum P (2000) Improving the efficiency of cardiopulmonary resuscitation with an inspiratory impedance threshold valve. *Crit Care Med* 28: N207–N209
27. Lurie KG, Zielinski T, Voelckel W, McKnite S, Plaisance P (2002) Augmentation of ventricular preload during treatment of cardiovascular collapse and cardiac arrest. *Crit Care Med* 30:S162–S165
28. Plaisance P, Lurie KG, Payen D (2000) Inspiratory impedance during active compression-decompression cardiopulmonary resuscitation. *Circ* 101: 989–994
29. Raven PB, Potts JT, Shi X (1997) Baroreflex regulation of blood pressure during dynamic exercise. *Exerc Sports Sci Rev* 25:365–390
30. Rowell LB (1986) *Human Circulation Regulation During Physical Stress*. New York: Oxford University Press, chapt. 7, pp 147–148
31. Rowell LB (1993) *Human Cardiovascular Control*. New York: Oxford University Press, chapt. 11, pp 409–413
32. Samniah N, Voelckel WG, Zielinski TM, McKnite S, Patterson R, Benditt DG, Lurie KG (2003) Feasibility and effects of transcutaneous phrenic nerve stimulation combined with an inspiratory impedance threshold in a pig model of hemorrhagic shock. *Crit Care Med* 31:1197–1202

Copyright of Clinical Autonomic Research is the property of Springer - Verlag New York, Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.

Copyright of Clinical Autonomic Research is the property of Springer Science & Business Media B.V. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.