Inspiratory Resistance as a Potential Treatment for Orthostatic Intolerance and Hemorrhagic Shock

VICTOR A. CONVERTINO, WILLIAM H. COOKE, AND KEITH G. LURIE

MAINTENANCE of consciousness requires adequate perfusion to the brain, which may be compromised in a variety of physiological and clinical circumstances. Insolvency to tolerate upright standing posture due to development of severe orthostatic hypotension and syncope often plagues astronauts and military personnel in their austere operational environments. In the civilian sector, up to 30% of otherwise healthy young adults report at least one syncopal episode during their lifetimes, and syncope accounts for up to 3% of all emergency room visits in the United States (31). More critically, hemorrhagic shock remains a leading cause of death in both civilian and battlefield trauma (7). Syncope and hemorrhagic shock share the same underlying mechanisms, namely, central hypovolemia and cardiovascular decompensation. A countermeasure that functionally restores central blood volume would, therefore, be expected to prove useful for all of these conditions.

Battlefield injury often leads to hypovolemia through hemorrhage. In spaceflight, hypovolemia occurs as a response to microgravity over the first several days of exposure (15,29), persists regardless of flight duration, and contributes to postflight orthostatic intolerance and reduced exercise capacity (16,33). The usual countermeasures for all of these conditions include fluid replacement (resuscitation) and/or lower body counterpressure (shock trousers or G-suits). For spaceflight, these often fail to prevent symptoms of cardiovascular instability or even frank syncope on assuming an upright body position at 1 G (5). Tolerance for loss of central blood volume or orthostatic stress can be enhanced by means of centrifuge training (24) and maximal exercise bouts prior to orthostatic testing (23), but these procedures cannot be applied in spacecraft and remote settings or medical evacuation aircraft.

Low central blood volume contributes to a reduction in cardiac filling, stroke volume (SV), and arterial pressure (P a). The resulting acute hypotension activates autonomically mediated compensatory mechanisms that evoke sympathetic nerve activity, tachycardia and peripheral vasconstriction in an attempt to restore P a (10). When the reduction in blood volume and P a reach a critical level, activation of compensatory mechanisms results in sympathetic withdrawal, bradycardia and vasodilation (10), a condition we refer to as circulatory collapse (11,19). Cardiovascular decompensation is the precursor to syncope or hemorrhagic shock. Therefore, any therapeutic approach that is designed to increase venous return and SV should counteract circulatory collapse. Increased negative intrathoracic pressure during spontaneous inspiration represents a natural mechanism for enhancing venous return and cardiac filling. Any device that applies resistance during inspiration takes advantage of this simple concept and shows promise as a mechanical facilitator of the respiratory pump that enhances venous return and pres Flight.
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to the heart (35,38,44). In this review, we examine a series of experiments designed to evaluate the effects of resistance devices on the clinical outcome of patients with chronic obstructive pulmonary disease (COPD) or other conditions in which airway resistance plays a significant role. The devices are classified as either positive or negative resistive devices, depending on whether they increase or decrease airway resistance, respectively. The positive resistive devices are designed to increase the work of breathing and thus reduce the work of the respiratory muscles, while the negative resistive devices are designed to decrease airway resistance and improve lung inflation. The effects of these devices on respiratory mechanics, gas exchange, and clinical outcomes are reviewed in detail.

Using the Chest as an Active Vacuum Pump

Cournand et al. (29) reported in an early study that venous return, ventricular preload, and subsequently cardiac output (Q) decrease with positive pressure breathing sufficient to maintain mean airway pressure. Guyton et al. (28) characterized the entire venous return curve in animals by plotting blood flow against pressure in the right atrium, as demonstrated by marked increases in venous return when right atrial pressures were reduced to -2 to -4 mmHg. Based on this simple concept of positive vs. negative intrathoracic pressures and their effects on venous return, it has been shown that increasing negative intrathoracic pressure through resistive breathing decreases left ventricular and right atrial pressures (38), consequently increasing left ventricular preload and SV index (59). The central hemodynamic response of resistive breathing is similar to that observed during Mueller maneuvers, where initial reductions of Pj due to reductions of left ventricular SV are followed by increases in Pj, due to resulting increased venous return and consequent increases in left ventricular SV (25,41).

Negative intrathoracic pressure during the inspira-
tion may be enhanced in several ways. In the experi-
ments described here, a controlled level of inspiratory negative pressure was produced in humans using an inspiratory threshold device (ITD) comprised of a plast-
ic valve attached to a standard clinical facemask (56). Responses to ITD breathing were compared directly with a sham ITD device which provided zero inspira-
tory pressure (ZTD).

Central Hemodynamics

Changes of central hemodynamics in humans during resistive breathing were assessed in two human studies (13,14). During spontaneous breathing in the supine position, inspiratory impedance of approximately 6 cm
H2O increased heart rate (HR), Pj (15,14), SV (measured with thoracic bioimpedance) and Q, and decreased total peripheral resistance (TPR) (14). Other countermea-
sures that restore central blood volume and protect SV and Q such as maximal inspiratory effort and load, and centrifugation technique may slow or reverse effects of alterations in central blood volume and hemodynamics similar to resistive breathing (24).

Autonomic Function

Although loss of blood volume contributes to post-
flight orthostatic intolerance in astronauts, reduction in the sensitivity of the baroreceptors in the carotid sinus has also been implicated in hemodynamic instability following both simulated (17,21) and actual microgravity (26,27). Carotid-cardiac baroreflex function is restored in sub-
jects after bed rest with application of maximal exercise 24 h prior to reanimation (23). Similarly, reductions of carotid-cardiac baroreflex sensitivity and reductions of central blood volume during lower body negative pressure (LBPN) are reversed with restoration of central volume during G-suit inflation (22). Stimulation of arterial and/or carotid baroreceptors by oscillations in intrathoracic or arterial pressure (25) may acutely change the sensitivity of the carotid-car-
diac baroreflex response (Rj) and affect automatic compensation to orthostatic or hypovolemic challenges. The effects of inspiratory resistance on the carotid-cardi-
cardiac baroreflex response were also tested in guinea pigs. During ITD breathing, carotid baroreflex sensitivity was not altered but responses were shifted to higher arterial pressures (13). With the initial work (14), support the hypothesis that negative intrathoracic pressure and baroreflex resetting induced by ITD breathing augments central hemodynamics and potentially increases the operational range of the baroreflex under conditions of severe hypotension.

Increased HR in conjunction with muscular contraction manifest through atrial stretch and activation of cardio-
pulmonary baroreceptors, but cardiopulmonary barore-
flex activity and consequent interaction with arterial baroreceptors during inspiratory resistance can only be inferred and not measured directly in humans; it is likely that both cardiopulmonary and arterial barore-
flexes operate to some degree and probably function at times in opposition (2). In addition, elevated HR and Q during spontaneous breathing on an ITD may simply reflect an "exercise" effect from the increased work of breathing against resistance. If this were true, one might expect withdrawal of vagal activity and no change or a slight increase in sympathetic activity with HR below 100 bpm (43). However, in experiments designed to test the mechanism(s) involved in the tachycardic response to inspiratory resistance, there was no change in venti-
latory mechanics (volume and rate), metabolic rate, car-
diact activity as indicated by no effect on the percent of normal consecutive R-R intervals that vary by more than 50 ms (pNN50), and muscle sympathetic nerve activity (microneurography) (13). While that re-
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sponse as a result of enhanced cardiac filling (e.g., the Bainbridge reflex, stretch of the SA node (1,24,2)).

Head-up tilt table experiments in astronauts prior to and immediately after the NASA Neurolab Space Mission (STS-97) produced an increased muscle sympathetic nerve activity (MSNA) induced by moving from the su-
pine to upright posture was associated with a reduction in SV (54). Although this finding was not unexpected, liter-
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exposure to 60 mmHg LBNP with normal breathing followed by use of an ITD (Convertino VA, et al. Unpublished communication; 2004). In this case, the LBNP caused a 30–35% reduction in SV, while the ITD produced an immediate increase that overshot and then returned to baseline after 1 min. If such results are confirmed, the ITD might provide a critical bridge for maintaining PaO2 in the face of hemorrhage until volume replacement can be provided. Thus, the ITD may provide trauma patients and mass casualties with effective and continuous combat care, especially for a bleeding patient with a weak or absent pulse.

SUMMARY

Countermeasures that increase central volume, re- store or support adequate autonomic function, and in- crease or maintain cerebral perfusion should be effec- tive in protecting against severe hypotension leading to syncpe and/or hemorrhagic shock in astronauts and victims of severe trauma. Approaches developed through space research can be used as fluid loading, use of G-suits, maximal exercise, and centrifuge training have been applied and have met with varying degrees of success. The primary limitation of such countermea- sures is lack of practical utility in an operational setting. This review shows that inspiratory resistance may be an effective alternative to the existing methods and can be im- plemented using a device such as the ITD, which is small and lightweight enough to be carried in austere medical kits. Such devices could be used to reduce postface orthostatic hypotension in astronauts, and to support brain perfusion in victims of severe traumatic blood loss.

ACKNOWLEDGMENTS

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7. Ide K, Klas, Poulin M. The relationship between middle cerebral artery blood velocity and end-tidal CO2 in the hypovolemia (32), the ability of the ITD to reduce hypotension and damage to the brain. These findings were confirmed in pigs that underwent cardiac arrest in 1999 and 2001. The ITD was found to be effective in reducing cerebral perfusion pressure (CPP), which is a critical factor in the outcome of patients who undergo cardiac arrest.

Fig. 1. Recording of neurograms from a subject during spontaneous breathing on a ZIT without inspiratory resistance (upper panel) and on an ITD (bottom panel). (From Convertino et al. [13].)

average SV and greater mean arterial pressure (MAP) measured during spaceflight in both supine and upright posture were pos- sitioned in a linear regression on the same SV-MAP rela- tion. The ITD was effective in reducing the incidence of syncpe associated with hypotension [34]. Using LBNP as a model for the investigation of mechanisms associated with hemorrhagic shock (19), we correlated the relationship between SV and MAP. (10, 11).

Fig. 2. A comparison of cardiac filling (40) and SV (14), spontaneous inspiration on the ITD lowered TPR (14). Since higher SV and lower TPR are associated with lower MAP in a linear fashion (10, 11, 34), it seemed possible that spontaneous breathing on an ITD would have no effect on supine MAP (15 = 8 ± 1.5 + 9 ± 0.05 bar/s/min) despite significant increases in mean arterial pressure (MAP) (94 ± 7 to 99 ± 19.5 mmHg) in eight normotensive, nonmedical subjects (18). In one subject, a 23-mL increase in SV (measured with thoracic bioimpedance) during ITD breathing was associated with an increase in MAP of 23.0±4.0 mmHg, with 30 bar/s/min during ventilation on the TID (Fig. 1).

These preliminary results support the hypothesis that elevated SV might produce proportionate reductions in MAP. MSNA and SNA responses in the coronary circulatory system during prolonged (23)–25) Mueller maneuvers and documented a biphasic response consisting of initial suppression of sympathetic traffic. These results verified the hypothesis that increasing SV and MAP during inspiration can be associated with the development of new sympathetic traffic during resistive breathing. Since high sympathetic nervous activity is associated with poor clinical outcomes in states of central hypovolemia, the ability of the ITD to reduce hypotension and damage to the brain. These findings were confirmed in pigs that underwent cardiac arrest in 1999 and 2001. The ITD was found to be effective in reducing cerebral perfusion pressure (CPP), which is a critical factor in the outcome of patients who undergo cardiac arrest.

Cerebral Blood Flow

In a porcine model of cardiac arrest, cerebral blood flow (CBF) and neurological function were significantly protected by application of an ITD [25].et al. demonstrated in pigs that ITD breathing would increase cerebral perfusion pressure (CPP), and increases CPP during cardiopulmonary resuscitation after cardiac arrest. Fig. 2 shows a representative example of the changes in intrathoracic pressure measured in the trachea of the pig, and concurrent changes in intracar- dinal pressure (ICP) measured in the brain parenchyma (Lurie KG, et al. Unpublished communication; 2004).

In this case, positive pressure ventilations were deliv- ered every 8 s and after each breath. Use of an ITD in conjunction with positive pressure breathing generated an intrathoracic pressure of ~0.10 mmHg and an immediate decrease in ICP by about 7.5 mmHg. The ITD also in- creased PaO2 (not shown). When the ITD was removed, ICP returned immediately to baseline levels. The impact of both ITD and positive pressure ventilation on ICP suggest a remarkable degree of concordance between changes in intrathoracic and cerebral perfusions, which may have significant implications in the treatment of a number of disorders that alter CPP. These new findings also suggest that the vacuum created by the ITD causes a "waterfall" effect that increases blood flow by maximizing the pressure gradient across the cerebral circulation. Maintaining adequate CPP while reducing ICP could prove critical in
prolonging or even preventing the progression to circulatory collapse associated with syncope and/or hemorrhagic shock.

Since inadequate cerebral perfusion ultimately leads to syncope and circulatory collapse (4), a device or procedure that effectively maintains or increases CBF might benefit returning astronauts or bleeding patients awaiting definitive medical care. Based on evidence from animal experiments (35,37,46) and the observation that subjects reported less severe symptoms (e.g., dizziness) during transition from the squat to standing posture (12), the effects of ITD breathing on CBV were investigated in humans. Cerebral blood flow velocity (CBFV) was recorded in the right middle cerebral artery in seven subjects using transcranial Doppler ultrasonography. Fig. 3 shows a representative response recorded from one subject.

For all seven subjects, breathing through an ITD increased mean CBFV from 64 cm/s to 69 cm/s during breathing on a ZTD by 69 cm/s during ITD breathing (p = 0.01). End-tidal CO2 for ITD breathing was 4.8 ± 0.1%, similar to that produced by the ZTD (4.9 ± 0.2%) (18). However, it is possible that increased respiratory drive during ITD breathing increased cerebral metabolic activity and therefore induced cerebral vessel dilation. The pulsatility index, an indirect estimate of cerebral vascular resistance tended to decrease with active ITD breathing (p = 0.09). The pulsatility index (calculated as the difference between peak systolic and end diastolic flow velocity divided by mean flow velocity) is clearly an imperfect estimate of cerebral vascular resistance that does not take into account systemic arterial, venous, or cerebral-spinal fluid pressures. However, in a prospective study of brain-injured patients, Bellner et al. (5) found a strong correlation (r = 0.94; p < 0.0001) between ICP measured by intraventricular catheter and the pulsatility index; they concluded that the latter is a useful surrogate for ICP for monitoring severely brain injured patients. Because end-tidal CO2 is an imperfect predictor of Pco2 (45), and because even small changes in Pco2 profoundly affect CBV (29), it is possible that the observed increases in CBFV during ITD breathing resulted from increased cerebral metabolic activity and consequent dilation of the cerebral vasculature.

Orthostatic Stress

Respiratory breathing might be expected to protect central hemodynamics against circulatory collapse induced by sudden orthostatic stress or hemorrhage (13-14). One study has addressed this possibility experimentally (12): 18 healthy normotensive volunteers (9 men, 9 females), ages 23-56, completed two 6-min protocols in counterbalanced order with a ZTD or an ITD set to open at −7 cm H2O pressure. An infrared finger photoplethysmograph was used to make non-invasive measurements of HR, SV, Q, TPR, and MAP. Symptoms were recorded using a subject perceived rating (SPR) where 1 = normal and 5 = dizziness.

Movement from squat to stand reduced TPR by about 39% with or without the ITD, but the device affected other variables, as illustrated in one subject in Figs. 4 and 5. Using the ZTD, he experienced severe symptoms (SPR = 4) as his SV fell (Fig. 4). TPR was reduced and pulse pressure dropped to below 20 (Fig. 5). In contrast, the ITD prevented symptoms (SPR = 1), erased the acute, transient drop in SV (Fig. 4) and held pulse pressure at 60 mmHg (Fig. 5). The periodic increases in SV in Fig. 5 reflect the negative intrathoracic pressure induced by the ITD during inspiration.

On average for all subjects, MAP fell 36 ± 3 mmHg with the ZTD compared with −27 ± 4 mmHg with the ITD (p = 0.03) despite similar elevations in HR (15 ± 2 bpm, p = 0.39) SV changed by 38 ± 4% for ZTD vs.

Simulated Central Blood Loss in Humans

The effects of inspiratory resistance were tested in human volunteers subjected to LBNP as a model for acute reduction of central blood volume due to hemorrhage (19). Fig. 6 shows beat-to-beat SV measured with thoracic bioimpedance during baseline supine rest and
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On average for all subjects, MAP fell 36 ± 3 mmHg with the ZTD compared with 27 ± 4 mmHg with the ITD (p = 0.03) despite similar elevations in HR (15 ± 2 bpm, p = 0.38) SV changed by 8 ± 4% for ZTD vs. +2 ± 4% for ITD; the corresponding changes in Q were +10 ± 6% and +22 ± 5% (p < 0.004). The SPR was 1.4 ± 0.1 for ZTD vs. 2.0 ± 0.2 for ITD (p = 0.04). These results suggest that the ITD may defend against orthostatic hypotension and intolerance. Future experiments should address the effects of ITD breathing in subjects after a period of simulated microgravity or experimentally induced hypovolemia.

Simulated Central Blood Loss in Humans

The effects of inspiratory resistance were tested in human volunteers subjected to LBNP as a model for acute reduction of central blood volume due to hemorrhage (19). Fig. 6 shows beat-to-beat SV measured with thoracic bioimpedance during baseline supine rest and +40 mmHg LBNP and +40 mmHg LBNP + ITD.
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exposure to 60 mmHg LBNP with normal breathing followed by use of an ITD (Convertino VA, et al. Unpublished communication; 2004). In this case, the LBNP caused a 30–35% reduction in SV, while the ITD produced an immediate increase that overshoot and then returned to baseline after 1 min. If such results are confirmed, the ITD might provide a critical bridge for maintaining Pm in the face of hemorrhage until volume replacement can be provided. Thus, the ITD may allow trauma victims to maintain a condition for combat care, especially for a bleeding patient with a weak or absent pulse.

SUMMARY

Countermeasures that increase central volume, restore or support adequate autonomic function, and increase or maintain cerebral perfusion should be effective in protecting against severe hypotension leading to syncope and/or hemorrhagic shock in astronauts and victims of severe trauma. Approaches developed through the space research as fluid loading, use of G-suits, maximal exercise, and centrifuge training have been applied and have met with varying degrees of success. The primary limitation of such countermeasures is lack of practical utility in an operational setting. This review shows that inspiratory resistance may be an effective alternative to the methods and can be implemented using a device such as the ITD, which is small and light enough to be carried in austere medical kits. Such a device would allow for the reduction of postorbital orthostatic hypotension in astronauts, and to support brain perfusion in victims of severe traumatic blood loss.

ACKNOWLEDGMENTS

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average SV and greater MSNA measured after spaceflight in both supine and upright postures were positioned in a linear relationship on the same SV-MSNA relationship. TID showed an increase in SV and MSNA responses in the TID group in contrast to the control group. The results of this study suggest that TID may be an effective method of maintaining cardiac output during postural transitions and in situations where cardiovascular function is compromised.

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