RESTORATION OF CENTRAL BLOOD VOLUME: APPLICATION OF A SIMPLE CONCEPT AND SIMPLE DEVICE TO COUNTERACT CARDIOVASCULAR INSTABILITY IN SYNCOPE AND HEMORRHAGE

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INTRODUCTION

The inability to tolerate upright standing posture due to development of severe orthostatic hypotension and syncope is a clinical problem that has plagued astronauts and military personnel in their austere operational environments as well as millions of people worldwide. More critically, hemorrhagic shock remains a leading cause of death in both civilian and battlefield trauma. Central hypovolemia and cardiovascular collapse (insufficiency) are the common features shared by syncope and hemorrhagic shock. It is therefore clear that the development of an effective countermeasure against the onset of syncope or hemorrhagic shock should focus on the simple concept of functionally restoring central blood volume. Although replacing blood or fluids may be beneficial in a clinical setting, it can prove impossible in operational settings such as a spacecraft and battlefields.

One of the primary mechanisms that contribute to syncope or hemorrhagic shock is the reduction in cardiac filling and stroke volume (SV). Therefore, any therapeutic approach that is designed to increase venous return and SV should be an effective countermeasure against cardiovascular collapse. Increased negative intrathoracic pressure during spontaneous inspiration represents a natural mechanism for enhancing venous return and cardiac filling. Taking advantage of this simple concept, the development and application of a resistance device applied during spontaneous inspiration has been shown to cause an immediate increase in arterial blood pressure when applied in different animal and clinical models associated with significant life-threatening hypotension [12-16]. This device has been named the impedance threshold device (ITD; Fig. 1). With its design, the inspiratory resistance induced by the ITD results in a greater vacuum within the thorax during each inspiration, and subsequently enhances venous return and preload to the heart [12,14-16].

The purpose of this paper is to review observations made from a series of experiments in our laboratory that focus on affecting hemodynamic responses by application of an ITD during conditions of central normovolemia and hypovolemia in human subjects. Specifically, results from human subjects exposed to supine rest, orthostatic challenge, and central hypovoleniia will be used to provide insight into relationships between regulation of blood pressure and flow, and functional performance.

EFFECTS OF THE ITD ON CENTRAL HEMODYNAMICS AND CARDIAC BAROREFLEX FUNCTION

We first hypothesized that breathing through an ITD would be associated with increased SV, cardiac output (Q), cardiac baroreflex sensitivity (BRS), and blood pressure [4,5]. We tested this hypothesis by measuring hemodynamic and respiratory responses in 10 female and 10 male subjects during two separate ITD conditions: (a) breathing through a face mask with an ITD set
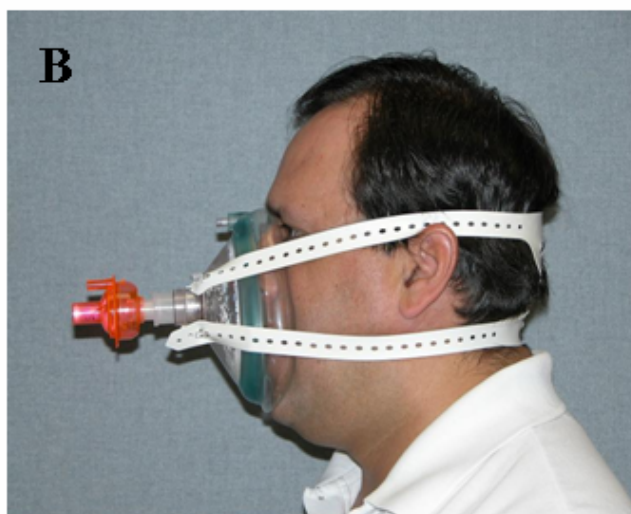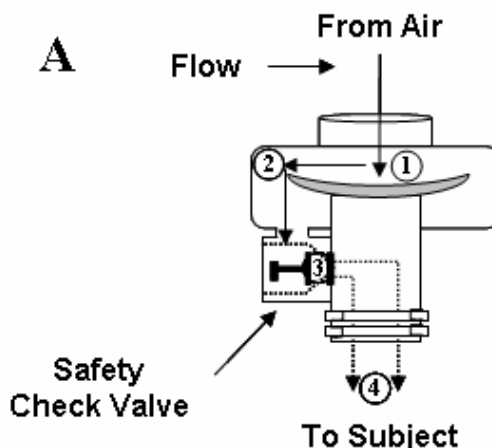

Fig. 1. Drawing illustration (top panel A) of the Impedance Threshold Valve (ITV). During spontaneous inspiration, air flow from the ventilation port to the subject causes the silicone diaphragm to close (Step #1). The air flow bypasses the diaphragm to the Safety Check Valve (Step #2). When intrathoracic pressure reaches and exceeds the impedance threshold of the valve, the Safety Check Valve opens (Step #3) and air reaches the subject (Step #4). Panel B (bottom) illustrates the ITD consisting of the ITV connected to a facemask.

at approximately -6 cm H_2O; and, (b) breathing through the same face mask with a sham ITD (control). The duration of ITD breathing was 14 min. The order of the two experimental conditions was counterbalanced, and each experiment was performed on a separate day. All hemodynamic measurements were repeated 5 min after cessation of ITD breathing. Compared with the control (sham) condition, an active ITD produced higher ($P < 0.05$) SV (124 ± 3 vs 137 ± 3 ml), HR (63 ± 3 vs 68 ± 3

bpm), Q (7.69 vs 9.34 liters/min), and systolic blood pressure (SBP; 115 ± 2 to 122 ± 2 mmHg) without affecting expired minute ventilation volume (6.2 ± 0.4 to 6.5 ± 0.4 liters/min). Compared with the sham device, the active ITD reduced (P = 0.003) total peripheral resistance (11.8± 0.4 to 10.0 ± 0.4 pru). During ITD breathing, BRS was not altered but responses were shifted to higher arterial pressures [4]. The absence of a reflex-mediated reduction in HR with increased SBP supports the notion of a resetting of the cardiac baroreflex. There were no gender effects and all hemodynamic responses returned to control (sham) levels by 5 min after cessation of ITD breathing. These results support the hypothesis that additional negative thoracic pressure and baroreflex resetting induced by ITD breathing at relatively low resistance can elevate arterial blood pressure by increasing HR, SV and Q [4,5].

EFFECT OF THE ITD ON RESPIRATORY WORK

We could not dismiss the possibility that elevated HR and Q 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 or a slight increase in sympathetic activity with heart rate below 100 bpm [17]. To test this hypothesis, we initiated subsequent experiments in an attempt to understand the mechanism(s) involved in the tachycardic response to ITD [8]. Contrary to the notion that the elevation of HR during use of an ITD represents a response to exercise, our results demonstrated no change in ventilatory mechanics [4], metabolic rate [4], cardiac vagal activity as indicated by no effect on the percent of normal consecutive R-R intervals that vary by > 50 ms [9] and muscle sympathetic nerve activity (microneurography) [9]. These observations suggest that the elevation in HR is initiated by a mechanical rather than meta-bolic 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).

EFFECT OF THE ITD ON CENTRAL HEMODYNAMICS DURING AN ORTHOSTATIC CHALLENGE

Based on the findings of the initial experiment, we hypothesized that the ITD may provide short-term protection against cardiovascular collapse induced by orthostatic stress or hemorrhage. In a subsequent investigation [6], we tested the effectiveness of an ITD as a countermeasure against the development of orthostatic hypotension during the transient phase of a squat-stand test. Eighteen healthy, normotensive volunteers (9 males, 9 females), ages 20-56, completed two counterbalanced 6-min protocols with and without (sham) an ITD set to open at -7 cm H_2O pressure. HR, SV, Q, total peripheral resistance (TPR), and mean arterial pressure (MAP) were measured non-invasively with infrared finger photoplethysmography (Portapres) during transition from squat-to-stand positions (SST). Symptoms were recorded on a 5-point scale (1 = normal; 5 = faint) of subject perceived rating (SPR).

Movement from the squat to the standing posture caused an average reduction of 35% in TPR with and without inspiratory impedance. When subjects breathed through a sham (no resistance control) device, a transient reduction in SV of approximately 50% occurred [6]. An example of a typical reduction in SV was reported coincident with a decrease in blood pressure from 168/93 to 88/48 and pulse pressure from 75 to 40 [7]. Subjects expressed

symptoms as severe as SPR = 4. When subjects breathed through an active ITD, SV was maintained during the transient phase of standing and increased during 1 to 2 minutes after the initiation of standing. Although blood pressure was decreased while breathing through an active ITD, pulse pressure was maintained [7]. As a group, average reduction in MAP with an active ITD during the transient phase of the SST (-27 ± 4 mmHg) was less (P = 0.03) than that measured while breathing on a sham device (-36 ± 3 mmHg) despite similar (P = 0.93) elevations in HR of 15 ± 2 bpm. Alterations in SV (+2 ± 4 %) and Q (+22 ± 5 %) with the active ITD were more positive (P = 0.04) than those measured with the sham ITD (-8 ± 4 % and -10 ± 6 %, respectively). SPR was 1.4 ± 0.1 with an active ITD compared to 2.0 ± 0.2 with the sham device (P = 0.04). Therefore, we demonstrated for the first time that reduction in orthostatic symptoms with application of an ITD is associated with an attenuated hypotension by increasing SV and Q. Our results demonstrated the potential application of an ITD as an effective clinical therapeutic aid against orthostatic hypotension and intolerance.

EFFECT OF THE ITD ON CEREBRAL BLOOD FLOW

In a porcine model of cardiac arrest, cerebral blood flow and neurological function were significantly protected by application of an ITD [12,13]. Based on these animal experiments and the observation that our subjects reported less severe symptoms (e.g., dizziness) during their transition from the squat to standing posture, we considered the possibility that breathing on an ITD increased cerebral blood flow. To test this hypothesis, we recorded cerebral blood flow velocity (CBFV) in the right middle cerebral artery in seven subjects using transcranial Doppler ultrasonography [8]. For all seven subjects, breathing through an ITD increased mean CBFV by 10% (P = 0.01). It is unlikely that changes in cerebral CO_2 caused the higher CBFV during ITD treatment since an active ITD produced an end-tidal CO_2 (4.8 ± 0.1 %) that was similar to that produced by breathing on a sham device without resistance (4.9 ± 0.2 %). Mean arterial pressure in these subjects was elevated by 4 mmHg with an active ITD (P = 0.05).

The mechanisms underlying increased blood flow to the brain with negative intrathoracic pressures remain under investigation. Recent data demonstrate that use of the ITD causes a decrease in intrathoracic pressure and an increase in HR, Q, and MAP. Preliminary data from our animal laboratory have further demonstrated that decreased intrathoracic pressure caused immediate reductions in intracranial pressure (ICP), both in spontaneously breathing animals during inspiration through the ITD and in apneic pigs in hemorrhagic shock [7]. In the apneic pig studies, the ITD was modified to enable the rescuer to set the pressure in the thorax to -10 mmHg but provide periodic positive pressure ventilation to maintain adequate gas exchange. Use of the modified ITD generated an intrathoracic pressure of -10 mmHg and an immediate decrease in ICP by about 7.5 mmHg. This also resulted in an immediate increase in arterial pressure. When the ITD was removed, ICP returned immediately to baseline levels. The impact of both the modified ITD and positive pressure ventilation on ICP suggest that there is a remarkable degree of concordance between changes in intrathoracic and intracranial pressures, which may have significant implications in the treatment of a number of disorders that alter cerebral blood flow. 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 cerebral blood flow while reducing intracranial pressure could prove critical in prolonging or even

preventing the progression to cardiovascular collapse associated with syncope and or hemorrhagic shock.

EFFECT OF THE ITD ON SYMPATHETIC NERVE ACTIVITY

Head-up tilt table experiments conducted in astronauts prior to and immediately after the NASA Neurolab Space Mission (STS-90) revealed that increased muscle sympathetic nerve activity (MSNA) induced by moving from the supine to upright posture was associated with a reduction in SV [11]. Although this finding was not unexpected, lower average SV and greater average MSNA measured after space flight in both supine and upright postures were positioned in a linear fashion on the same SV-MSNA stimulus-response relationship as the average pre-flight SV and MSNA responses [11]. Using lower body negative pressure (LBNP) as a model for the investigation of mechanisms associated with hemorrhagic shock [9], we corroborated the linear relationship between SV and MSNA [2,3].

In addition to increasing cardiac filling [16] and SV [5], spontaneous inspiration on the ITD lowered TPR [5]. Since higher SV and lower TPR are associated with lower MSNA in a linear fashion [2,3,11], we hypothesized that spontaneous breathing on an ITD would cause a reduction in MSNA. To test this hypothesis, we measured SV (infrared finger photoplethysmograpy) simultaneously with MSNA in 8 subjects during two separate ITD conditions: (a) breathing through a face mask with an ITD set at approximately -6 cm H_2O; and, (b) breathing through the same face mask with a sham ITD (control) [8]. The duration of ITD breathing was 3 min and the order of the two experimental conditions was counterbalanced. Unfortunately, we failed to produce any statistical difference in the average SV or MSNA during spontaneous breathing on the ITD in these eight normovolemic, normotensive subjects. However, individual data were encouraging. A 23-ml (25%) increase in SV measured in one subject during ITD breathing was associated with an MSNA of 23 bursts/min compared to 30 bursts/min when breathing on the sham device [7]. These preliminary results support the hypothesis that given substantially large elevations in SV, we might expect proportionate reductions in MSNA. Since high sympathetic nerve activity is associated with poor clinical outcome in states of central hypovolemia [10], the ability of the ITD to reduce SNA could prove important as an effective countermeasure against syncope and hemorrhagic shock. Future experiments designed to induce more dramatic alterations in central hemodynamics are planned to test this hypothesis.

EFFECT OF ITD APPLICATION DURING SIMULATED CENTRAL BLOOD LOSS

The successful development and deployment of a device designed to immediately increase blood pressure following the onset of hypovolemic shock from hemorrhage or dehydration would prove to be an important advance in treating civilian and battlefield casualties.

With evidence that inspiratory resistance creates a vacuum within the chest drawing blood from the extrathoracic venous system into the heart of animals in hypovolemic shock [14] and each time resting normal human volunteers take a breath [5], we considered the possibility that an ITD might prove effective in restoring central blood volume, venous return and SV during severe reduction in central blood volume similar to hemorrhage. To test this hypothesis, we have initiated experiments using LBNP as a model to reduce central blood volume in human subjects. We

have demonstrated that LBNP provides a technique for inducing hemodynamic and autonomic responses similar to those that occur in actual hemorrhage [9]. We propose to measure cardiac filling (echocardiology), HR, SV, Q, arterial blood pressures, and MSNA in healthy human subjects while they undergo exposure to LBNP designed to determine their tolerance (i.e., induce cardiovascular collapse). The tolerance endpoint to central hypovolemia will be determined by any one or combination of the following criteria: (a) onset of symptoms such as grey-out, a precipitous fall in SBP greater than 15 mmHg, and/or a sudden bradycardia greater than 15 bpm between adjacent 1-min measurements; (b) progressive diminution of SBP below 70 mmHg; and (c) voluntary subject termination due to symptoms such as sweating, nausea, or dizziness. Subjects will complete the following two experimental sessions: (a) during spontaneous breathing through a face mask with the use of the ITD set at approximately -7 cm H_2O; and (b) during a control (breathing through the same face mask with a sham ITD) session.

Figure 2 shows the effectiveness of ITD breathing during severe central hypovolemia. The upper panel of Figure 2 depicts a subject breathing on a sham ITD during a presyncopal episode (occurrence at ~ 2,360 seconds) induced with application of 90 mmHg LBNP. The lower panel of Figure 2 shows this same subject on a different day breathing on an active ITD. These data show clearly the mechanical effects on inspiratory resistance, as pressures rose and fell in conjunction with the respiratory cycle. During both experiments, LBNP was applied progressively with identical time courses, and breathing through an active ITD allowed this subject to progress beyond 90 mmHg to 100 mmHg (increased tolerance of ~ 90 seconds at a greater central blood volume reduction).

These preliminary results suggest that the application of an ITD during acute treatment of hemorrhage may provide a critical bridge to more definitive repair of the primary injury and ultimate survival. Certain medical emergencies such as acute hemorrhage require immediate treatment before intravenous access and therapy is available. As such, our data support the notion that the ITD may have an important role in civilian trauma patient and tactical combat care, especially in the setting of a wounded soldier with a weak or absent pulse.
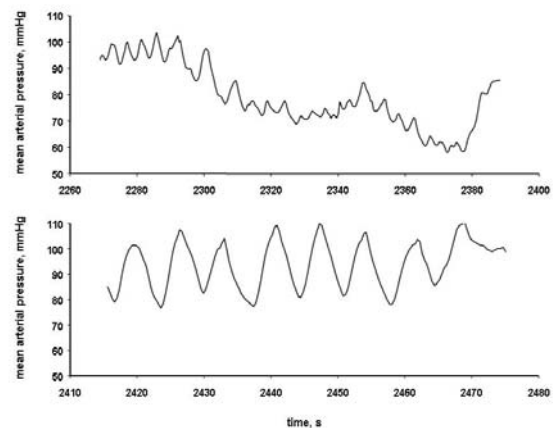

Fig. 2. Beat-to-beat mean arterial pressure of a subject during exposure to severe reduction in central blood volume induced by LBNP while breathing on a sham ITD (top panel) and an active ITD (bottom panel).

CLINICAL APPLICATIONS OF THE ITD

Cardiac Arrest. Use of an ITD increases circulation and neurologically intact survival in models of cardiopulmonary resuscitation (CPR) of animals [12,13]. As a result, studies have been initiated [1] to evaluate the ITD in patients with out-of-hospital cardiac arrest during standard manual CPR (sCPR). A prospective, randomized, double-blind trial was conducted in an urban emergency medical services system. Adults in cardiac arrest were randomly assigned to active or sham ITD groups and survival outcomes were recorded. The primary endpoints were SBP and intensive care unit (ICU) admission rate. In a subgroup of subjects (N = 11), SBP increased (P = 0.05) with the active ITD (91.5 ± 10.3 mmHg) compared to the sham ITD (59.5 ± 9.5) while DBP was unaltered (active ITD = 23.0 ± 15.8 mmHg versus sham ITD = 20.9 ± 9.3 mmHg). Overall, rates for 1-h survival, ICU admission, and 24-h survival were not statistically distinguishable between patients who used the sham ITD (n=116) compared to those who used the active ITD (n=114). However, in a subgroup of patients presenting with pulseless electrical activity (PEA) at any time during the resuscitation effort who used the active ITD (n=49), rates for 1-h survival, ICU admission, and 24-h survival were higher (P < 0.04) compared with patients (n=56) who used a sham ITD (Fig. 3). In patients with ventricular fibrillation/tachycardia initially, 1-h, ICU admission, and 24-h survival rates were not statistically different between the sham ITD (n=3l) and the active ITD (n=28). Outcomes were similar for patients with asystole. The ITD had the greatest impact survival rates in the subgroup of patients who had PEA at any time but did not have an initial recorded rhythm of asystole. No significant adverse events were reported.

In patients with PEA during CPR, the arterial pulse was palpable and >90 mmHg. When CPR was stopped, the pulse was no longer palpable but a small increase in systolic blood pressure could often be observed in the arterial blood pressure waveform with each ventricular depolarization associated with electrical activity. In other words, the pulse was present concurrently with electrical activity but the pulse was too weak to be felt and could only be seen with invasive monitoring. This physiology is identical to that of a patient with a severe hemorrhage. In this setting the ITD had a profound impact on acute survival rates.

Use of an ITD during sCPR in patients with out-of-hospital cardiac arrest significantly increased SBP and more than doubled short-term survival for patients with PEA at any time during the resuscitation effort. These preliminary results represent the first effective treatment to increase acute resuscitation rates for patients in PEA. Larger investigations are planned to determine the potential long-term benefits of the ITD and sCPR for the treatment of cardiac arrest.

Clinical Orthostatic Hypotension. Orthostatic intolerance is an important clinical problem with few treatment options. To evaluate a new therapeutic approach, the potential benefit of an ITD for attenuating posturally-induced blood pressure (BP) reductions was examined in patients with a known history of orthostatic hypotension. Patients were randomized to either an active (impedance = -7 cm H_2O) or a sham ITD. BP, HR, and SV were recorded using a Portapres noninvasive monitor. Continuous beat-to-beat monitoring was undertaken as each subject first breathed through the ITD for 30 s while lying supine, and then for an additional 30 s after standing upright. One hour later, the test was repeated with the alternate ITD (i.e., active or sham) to that used first. Hemodynamic benefit was defined as a reduction of 20% in maximum standing-induced BP fall with active vs. sham

ITD. Symptoms were assessed using a 10-point scale: 0 (None) to 10 (Severe). Nineteen patients (12 females) aged 18 to 56 years (mean 37.6 years) were enrolled. The ITD reduced postural BP fall in 8 patients (responders, 42%), and had no hemodynamic benefit in 11. Comparing active to sham ITD in responders, the maximum drop in SBP, DBP, and SV at 30 s after standing was 11% vs 29% (p = 0.02), 18% vs 39% (p = 0.01), 21% vs 26% (p = 0.30). Maximal rise in HR was 31% vs 35% (p = 0.34, active vs sham). Symptom status was similar in active or sham tests, suggesting no significant adverse ITD effects. Patients who had a fall in BP at the time of the study when breathing through the sham device had a significant reduction in the fall in BP with the active ITD. Use of the active ITD reduced the fall in blood pressure by 50% when patients moved from the sitting to the standing position [15].
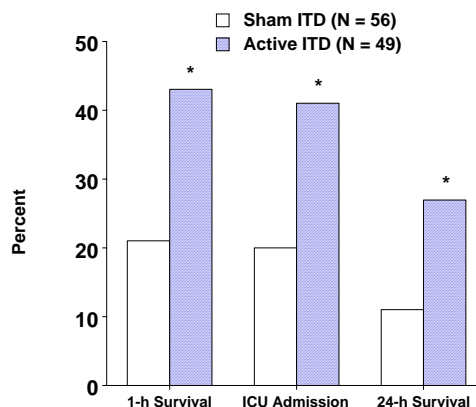

Fig. 3. Average rates for 1-h survival, ICU admission, and 24-h survival between cardiac arrest patients with pulseless electrical activity at any time who used a sham ITD (open bars) and an active lTD (solid bars). Asterisk indicates P <0.04 vs. sham value.

Hypotension during Renal Dialysis. Approximately 25% of patients undergoing chronic renal dialysis develop hypotension during the treatment. Two causes are thought to be responsible for the intradialytic hypotension: osmolar shifts as the blood urea nitrogen is removed within the first 30 minutes of dialysis and hypovolemia at the end of the run as often more than 3 L of fluid are removed on any given day. A pilot study was performed in 12 patients who developed hypovolemic hypotension during renal dialysis to test the hypothesis that augmentation of the negative intrathoracic pressure generated during inspiration using the ITD during an intradialytic hypotensive episode would elevate arterial blood pressure to a level that may reduce the need for further medical intervention [19]. All patients developed hypotension during their dialysis run. At the point that medical and nursing staff would normally treat the hypotension with current therapies such as administration of hypertonic saline, florinef, midodrine, or slowing the dialysis runs, the patients used the ITD for between 5 and 10 minutes when hypotension developed. The resistance of the ITD was between -6 and -8 cm H_2O. ITD treatment was discontinued after arterial pressure returned to baseline levels or if the ITD was not tolerated. The ITD was well tolerated in 11 of 12 subjects during an average exposure duration of 7.0 ± 1.5 min. SBP, DBP and MAP were increased (p < 0.001) by the use of the ITD (Fig. 4), while heart rate and respiratory rate were not affected by the ITD. In this first observational study in patients

with hypovolemic hypotension, use of an ITD during episodes of intradialytic hypotension rapidly and significantly increased blood pressure by >15 mmHg without an increase in heart rate or any observable adverse events. Based upon these highly successful outcomes, a larger randomized blinded clinical trial is underway in patients undergoing renal dialysis.
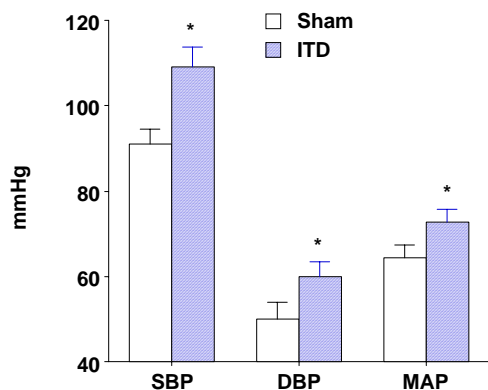

Fig. 4. Systolic (SBP), diastolic (DBP) and mean (MAP) blood pressure responses with a sham ITD (open bars) and an active ITD (solid bars) during renal dialysis. Values are mean ± SE (N = 12). Asterisk indicates P < 0.001 vs. sham value.

Hypotension after Blood Donation. A study was performed in 19 subjects after blood donation in an effort to examine the safety and efficacy of the ITD in patients with a small degree of hypovolemia. All subjects were healthy volunteers. Blood pressure was measured before and immediately after removal of a unit of blood at a local blood bank. Subjects were then randomized to either a sham or active ITD. After a 9-min application, the order of the devices was reversed. Blood pressure responses are presented in Figure 5. There was a statistically significant increase in blood pressure when the active ITD was applied as the initial intervention and a significant fall in blood pressure when it was removed. By contrast, when the sham ITD was used initially, the subjects' blood pressure did not change. Nine minutes later when the active ITD was applied, blood pressures increased and subsequently fell when it was removed. One subject, who was hypotensive after blood donation, had an increase in blood pressure when the ITD was applied and lost consciousness when the active ITD was removed. These results are consistent with other observations that use of the ITD is (a) safe and effective in increasing systolic blood pressures in subjects with acute central hypovolemia and (b) may require application for a longer period of time in some donors susceptible to syncope after blood donation in order to maximize the benefits of the ITD.

Based upon these recent data from laboratory experiments and clinical studies, we believe that the application of the ITD will provide an effective countermeasure against: (a) post spaceflight orthostatic hypotension in astronauts; (b) shock secondary to severe blood loss or heat; (c) hypotension secondary to orthostatic intolerance, dehydration, or renal dialysis; (d) treatment of right heart failure after myocardial infarction; (e) elevated intracranial pressure after head trauma; and (f) treatment of cardiac arrest. In each of these medical emergencies, rapid restoration of blood pressure is essential to maintain vital organ function. Intravenous access and fluids are not always available. Although fluid

resuscitation, once available, is often of clinical value, the ITD is able to help rapidly restore central blood volume by transforming the thorax into a more active vacuum, drawing venous blood from extrathoracic cavities into the heart and lungs, and lowering intracranial pressures and increasing cerebral blood flow.
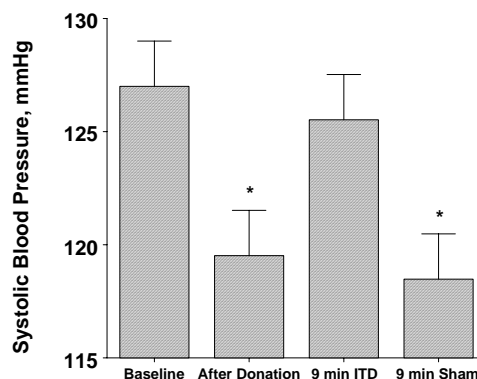

Fig. 5. Systolic blood pressure responses with an active ITD and sham ITD following blood donation. Values are mean ± SE (N = 19). Asterisk indicates P < 0.05 vs. baseline value.

In summary, the ITD is FDA-approved as a circulatory enhancer intended for the treatment of relative hypovolemia and hypotension suffered by people as a result of reduced central blood volume. The ITD is lightweight, easy to use, durable, relatively inexpensive, and well tolerated. It could be easily carried by an astronaut, added to a civilian or combat medic's bag, or could travel easily onto the battlefield with every soldier. As such, use of the ITD may "buy time" by providing a critical bridge to more definitive repair of the primary injury and ultimate survival.

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