ABSTRACT

Traumatic injuries are an everyday occurrence, from minor scratches to the massive injuries of auto accidents. Based on this reality NASA has prepared for a range of contingencies to care for injured astronauts. These preparations have been based upon the clinical incidence of traumatic injuries in environmental analogs such as Arctic habitats. However, information is needed as to the effect of acclimation to the space environment on responses to injury, subsequent treatment and rehabilitation. Deconditioning of a subject leads to significant alterations in responses to hemorrhage, susceptibility to infection, and the healing process. The treatment of the injured astronaut may have to be altered to compensate for the effects of acclimation in light of these findings. Furthermore, upon return to Earth's gravity therapeutic interventions, such as administration of anesthetics, may have to be adjusted. The response of patients to the deconditioning of acute bedrest associated with the care of traumatic injuries provides insight into care of injured astronauts. In order to assure the mission success of long duration space flights the care of even minor injuries should be extensively evaluated.

Traumatic injuries are often the result of a single acute event. However, the consequences of traumatic events can be far reaching, extending from the patient to families, communities, nations, and the world as a whole (Kauvar & Wade 2005). Spaceflight programs have not been immune to traumatic injuries. While most of these injuries have been lethal, space agencies have focused extensive resources on consideration of the traumatic injuries that may occur during the course of space flights. As the duration and planned scope of space flight missions is expanded the probability of traumatic injuries is increased. Of concern is the health and well being of the injured astronaut as well as the impact on mission success.

Epidemiology of Emergencies

Traumatic injuries take many forms, from the very simple scratch to the massive crush injury with broken bones and hemorrhage. The space agencies have focused on the injuries serious enough to be classified as emergencies, where the life of an individual or the success of a mission is threatened (Safe Passage: Astronaut Care for Exploration Missions 2005; Billica et al. 1996; Kirkpatrick et al. 2005, 1997; McCuaig 1994; McCuaig & Houtchens 1992; Summers et al. 2005). In the 44 years of manned spaceflight 5 major accidents have resulted in 21 deaths (Safe Passage: Astronaut Care for Exploration Missions 2005). Other accidents have resulted in traumatic injuries, but most of these have occurred on Earth where traditional emergency advanced life support measures were applied (Summers et al. 2005). During flight in the microgravity environment few medical emergencies have been documented, with only two reported incidents of traumatic injuries (Safe Passage:Astronaut Care for Exploration Missions 2005; Billica et al. 1996; Summers et al. 2005).

In the general population, the incidence of medical emergencies is 0.06 events per person year (Safe Passage: Astronaut Care for Exploration Missions 2005; Billica et al. 1996; Summers et al. 2005). Using this model, a ten member crew on a 2.4 year mission to Mars would have at least one medical emergency (10 people x 2.4 years x 0.06 incidence per person-year = 1.4 emergent medical events). It could be expected that the incidence in the extreme environment of space would be higher than the rate observed in the general population. However, studies conducted in different injury settings have helped to formulate the direction and policies of the NASA emergency medical program. These environments include the US Navy experience in nuclear submarines and the Antarctic McMurdo Station (Thomas et al. 2003; Lugg 2000). Estimates of the occurrence of medical emergencies during spaceflight are based on the data from these environments. At McMurdo Station the incidence of medical emergencies requiring medical evacuation is reported as 0.036 events per person-year (Lugg 2000). Review of the Russian program found four medical evacuations over 72 person-years in space with an incidence of 0.056, very similar to that of the general population (Summers et al. 2005). Thus both the data from spaceflight and simulation environments yield rates of 0.04 to 0.05 per person-year for a medical emergency requiring evacuation. In planning for long-duration spaceflight the probability of an emergent event must be considered and appropriate measures to deal with the situation must be in place.

There have been 17 medical emergencies during spaceflight in the NASA program, two of which were traumatic injuries (Safe Passage:Astronaut Care for Exploration Missions 2005; Summers et al. 2005). In the NASA program the incidence of emergencies related to trauma (12%) falls far below that observed in the McMurdo Station (48%) (Lugg 2000; Safe Passage: Astronaut Care for Exploration Missions 2005). Irrespective of the present rate of injury, traumatic injuries are of great concern to the NASA program as they...
are mentioned in 44% of the 45 risk areas in the Bioastronautics Critical Path Road Map (http://bioastroroadmap.nasa.gov/index.jsp). Further, five questions under the heading “Major Illness and Trauma” present the following:

18d) What resources are required for telemedical consultation, diagnosis, and management of major trauma?
18f) What are the resources and procedures needed to perform basic and advanced management of trauma?
18I) What procedures and protocols are necessary for rehabilitation after an acute medical illness or trauma?
18AH) What resources and procedures are needed for the surgical management of major illness, injury, and trauma?
20E) What are the resources and procedures required for the treatment of minor trauma, emphasizing autonomous decision-making, based on known space flight illnesses, injuries, and expedition analogs? How might they be adapted to reduced-G operations?

NASA has focused its efforts on applying the standard medical treatments used on Earth to spaceflight (Safe Passage: Astronaut Care for Exploration Missions 2005; Kirkpatrick et al. 2005, 1997; Summers et al. 2005). The agency has contributed significantly to the medical field by making equipment/devices simpler, smaller, and autonomous. Furthermore, efforts have been made to take into account the physical environment (microgravity, closed-loop environmental systems, etc.) when caring for the spaceflight patient. For example, alternatives to the use of volatile anesthetics and the means of restraint of the surgical patient have been evaluated (Campbell 2002, 1996, 2002, 2004, 2001). However, the physiological changes of the patient due to acclimation to the microgravity environment have not been adequately considered. In formulating and reviewing NASA’s policies regarding the care of the astronaut with an emergency due to traumatic injuries, the altered physiological status of the patient is recognized and the need for additional information noted. Though the problem is clearly defined it has not been adequately addressed.

The study of the care of traumatic injuries is conducted in animal models that provide evidence for the formulation of guidelines for treatment of human patients. The efficacy of the guidelines is then evaluated over the course of patient care. An example of this process is the study that led to the classification of astronauts as at risk when undergoing anesthesia. On the Bion 11 mission anesthetic complications occurred in two primates who had been in spaceflight for 14 days (Ilyin et al. 2000). This project was a multinational effort to study the effects of spaceflight on bone, muscle and the vestibular system. Anesthetic was administered to the animals by a competent team of veterinarians on the first day post-flight for minor surgery, muscle biopsies. One animal died during the procedure and the other experienced serious complications. Previously, surgeries had not been performed until the seventh day of recovery following Bion flights, and no complications were observed.

Furthermore, the procedure done multiple times on control animals produced no adverse events. This experience pointed out that the knowledge of risk imposed by anesthesia following acclimation to the spaceflight environment is limited (Safe Passage: Astronaut Care for Exploration Missions 2005; Norfleet 2000). This incident led to the reclassification of astronauts by the American Society of Anesthesiologists (ASA) 4: A patient with severe systemic disease that is a constant threat to life. The change in classification means increased vigilance when administering anesthetic to patients and during recovery. Another example of the value of animal studies in space was the series of surgical procedures performed on rats during Neurolab mission which confirmed the expectation that surgery can be conducted in microgravity (Safe Passage: Astronaut Care for Exploration Missions 2005; Campbell et al. 2005; Kirkpatrick et al. 2005). These examples of the findings derived from the study of animals subsequently impacted patient care. While these are anecdotal observations there is increased interest in establishing requirements for the acute care of astronauts by performing classically designed studies, as noted in a recent National Academy of Science (Safe Passage: Astronaut Care for Exploration Missions 2005) report: “Although it may not be realistic to replicate these myriad physiological studies during the postoperative period, carefully designed experiments with simple outcome measures (supplemented by highly selected physiological, histological, or metabolic studies) performed in a microgravity environment such as the International Space Station (ISS) after surgery in animals might yield significant information of value.”

Presented below is an example of how animal experimentation provides information to predict the possible impact of the microgravity environment on the care of astronauts with traumatic injuries. This example, fluid resuscitation in response to hemorrhage, was selected as it is part of the initial response to injury and was called out in the National Academy Report (Safe Passage: Astronaut Care for Exploration Missions 2005).

**Fluid Resuscitation in Response to Hemorrhage**

On Earth the care of the patient with severe traumatic injuries is compartmentalized into a series of care responses. The first responder, in most developed countries is a paramedic, who renders first aid assuring that the airway is open, there is adequate ventilation, and bleeding is controlled. Once this is accomplished, resuscitation is initiated, often entailing the administration of fluids. It is expected that in the course of a continued human presence in space a number of situations will require the use of resuscitation solutions. These include traumatic injuries, blood loss during surgery and a number of circumstances resulting in dehydration. At present the requirement for resuscitation fluids has not been documented in the space programs. However, one could assume that the need would be similar to those observed in other extreme environments such as submarines or Antarctica.
The primary use of resuscitation fluids in spaceflight would be associated with emergency and surgical procedures (Kirkpatrick et al. 2005, 1997). Emergency surgery might have to be performed in a variety of scenarios. While resuscitation fluids are mostly used as volume support in the course of a conventional surgery, the rate of blood loss could be greater during spaceflight as blood clotting may be compromised, and a trained surgeon may not perform the procedure. Thus, a greater amount of blood loss would be expected.

Attempts to evaluate the performance of surgery in microgravity generally concluded that operative procedures may be conducted (Safe Passage: Astronaut Care for Exploration Missions 2005; Campbell et al. 2005; Kirkpatrick et al. 2005). However, the limitations of the procedures were not defined. Fluid would also be required for the care of an astronaut requiring surgery immediately upon return to Earth for an emergency procedure. These two surgical environments may necessitate different types of fluids or different procedural approaches to fluid administration than those normally used.

Traumatic injuries may also occur in space. For example the ISS is a construction zone with astronauts often moving large objects during extravehicular activity (EVA or “space walk”). These activities are believed to be the riskiest for traumatic injuries. Though the utmost safety precautions are in place, the probability of injury is still high. These injuries could be both blunt and penetrating and could result in bleeding from an open wound or into a body cavity. On Earth hemorrhage is the leading cause of death due to traumatic injuries and accounts for 80% of intraoperative trauma deaths (Champion 2004; Sauaia et al. 1995). Fluids for the patient with traumatic injuries would stabilize the individual prior to definitive care, such as a surgical procedure, which would in turn necessitate further fluids.

Resuscitation solutions would also be used for the treatment of hypovolemia induced by dehydration. Astronauts spend extended periods of time doing work in space suits and in exercise with significant dehydration. It is conceivable that extreme dehydration could require the administration of fluids. Another likely cause of fluid loss would be food poisoning or gastroenteritis resulting in excessive diarrhea and vomiting, though oral rehydration has been demonstrated as the ideal means of replacement for gastrointestinal losses.

The goal of fluid administration for these conditions is hemostasis (correcting physiological parameters to normal levels). On Earth, accomplishing this goal is often difficult, time consuming and requires extensive resources. In spaceflight hemostasis for a victim of hypovolemia by fluid resuscitation may be insufficient or impossible to attain due to limited resources and expertise. A comprehensive review of resuscitation fluids for spaceflight by Kirkpatrick et al. (Kirkpatrick et al. 2005) reports that, “Present medical care in space has been developed on the basis of proven conventional terrestrial strategies of proven health care.” There has been no attempt to systematically evaluate resuscitation procedures or solutions to meet the unique requirements of the altered physiology of an astronaut acclimated to spaceflight.

Presently, normal saline (NS; 0.9% NaCl) is the primary solution carried aboard the Shuttle and the ISS. The total volume available is 4 L in the Advanced Life Support Pack (ALSP) and 7.5 L in the Health Maintenance System Ancillary Support Pack. The ALSP carries an additional 0.5 L of dextrose (D5W) (information provided by the NASA Crew Office). Therefore, the total available fluid is 12 L. For the care of a major traumatic injury this would equate to a blood volume expansion capability of only 4 L (American College of Surgeons, C. O. T. Advanced Trauma Life Support Student Manual (ATLS) 1997; Fluid Resuscitation: State of the Science for Treating Combat Casualties and Civilian Injuries. 1999). In a recent study of penetrating trauma we found the fluid requirements to be 12.5 L over the first 24 hours (Wade et al. 2003). Therefore, the volume and type of fluid presently stored on space vehicles appears insufficient.

In the administration of normal saline to critically injured patients it is recommended that the patient receive three times the volume of blood loss (American College of Surgeons, C. O. T. Advanced Trauma Life Support Student Manual (ATLS) 1997; Fluid Resuscitation: State of the Science for Treating Combat Casualties and Civilian Injuries.). However, the Advanced Trauma Life Support recommends the limitation of fluid administration to maintain systolic pressure to reduce uncontrolled bleeding and the use of normal saline has been questioned, as large amounts of fluid collect in the extravascular space (American College of Surgeons, C. O. T. Advanced Trauma Life Support Student Manual (ATLS) 1997). This “third spacing” has been implicated in subsequent morbidity, specifically, an increased incidence of multi-organ dysfunction and acute respiratory distress. Another risk factor in the use of large volumes of normal saline is the hemodilution of red cell mass that decreases oxygen carrying capacity and dilution of clotting factors that would result in secondary re-bleeding.

At present the various space programs recognize the need for resuscitation but specific requirements are not clearly defined. What is not understood is the impact of the space environment on the response of the patient to hypovolemia and the ability to adequately resuscitate the individual. The spaceflight environment presents a number of other challenges in the treatment of the patient with hypovolemia. These include alterations in the cardiovascular, endocrine, immune, and hemopoietic systems as well as metabolic changes coupled with the closed environment of the spacecraft. Below we present possible modulators to the response of hypovolemia and subsequent resuscitation. In addition we discuss the use of a ground-based animal model in light of these changes.
Based on the plethora of changes in spaceflight any studies on the ground should employ a model emulating as many of these alterations as possible. In human subjects this has been accomplished by extended periods of bed rest. While this model is appropriate for studying countermeasures and provides some information as to acute fluid shifts, the use of humans to evaluate hemorrhagic hypovolemia due to injury is not warranted. An animal model is the method of choice, especially if the influence of long-term acclimation to the spaceflight environment is to be evaluated.

The animal model we have focused on is the hind limb suspended (HLS) rat (Morey-Holton & Globus 2002). This model reproduces many of the characteristics observed in humans and rodents in response to spaceflight. In addition, if efficacy of resuscitation solutions is to be evaluated in the microgravity environment of spaceflight the rodent is the model specimen of choice. Rodents have an extensive flight history, and have been manipulated during spaceflight and have undergone surgical procedures. Thus, rats provide the basis for subsequent studies evaluating fluid resuscitation procedures and techniques in actual spaceflight.

**Response to Spaceflight: human vs. hind limb suspended (HLS) rat model**

Spaceflight results in pronounced changes in the physiology of astronauts and rodents. We will focus on the changes observed in the acclimated individual and do not discuss the acute responses before acclimation upon insertion into orbit. These changes have been extensively reviewed. We will use the reviews as a basis for the discussion of the impact of these changes on the ability to compensate for blood loss due to hemorrhage and the subsequent ability to resuscitate the patient. We will then address the response of the animal model and its viability as a surrogate to study the responses in astronauts.

**Cardiovascular changes**

*Hemodynamics:* The hemodynamic status of the astronaut once acclimated to space flight is relatively normal (Convertino 1996; Hargens & Watenpaugh 1996; Sawin 1998; Watenpaugh 2001). Blood pressure and heart rate are within normal limits. Some reports note decreases in resting heart rate, as well as a trend toward reduction in diastolic pressure. These changes have been highly dependent upon the flight mission and are within normal clinical variability. Rodents exposed to HLS have an initial period of acclimation similar to that of astronauts in spaceflight (Overton et al. 1989; Ray et al. 2001). Following this period mean arterial pressure (MAP), heart rate (HR), systolic arterial blood pressure (SBP) and diastolic blood pressure (DBP) seldom differ from those of control animals.

Cardiac output following acclimation to spaceflight is normal in astronauts (Hargens & Watenpaugh 1996). If there is a reduced heart rate there is an accompanying increase in stroke volume to sustain cardiac output. In the rat HLS model there is no difference in cardiac output at rest compared to control animals (Overton et al. 1989; Woodman et al. 1995). As with the astronauts, reduced responsiveness in cardiac output paralleled increasing exercise loads. Failure to increase cardiac output in the presence of increased metabolic demands as noted during exercise would not bode well for correction of the loss of oxygen-carrying capacity, and thus delivery, during hemorrhage or the subsequent hemodilution and volume expansion of resuscitation.

**Blood Volume:** Cardiovascular changes include a reduction in blood volume on the order of 15% in astronauts (Convertino 1996; Hargens & Watenpaugh 1996; Leach et al. 1996; Strollo 1999; Watenpaugh 2001). The decrease in blood volume occurs by reductions in both plasma volume and red cell mass, such that hematocrit is not changed. This decrease in blood volume could be detrimental upon return to Earth in the hypovolemic patient. With re-exposure to Earth’s gravity a shift in fluids has led to orthostatic hypotension necessitating countermeasures. It would be logical that the reduced blood volume would adversely impact a patient brought back to Earth exacerbating the hypovolemic state. In flight the reduced volume appears to be defended (see Fluid Homeostasis below). The blood volume of HLS animals appears to be reduced, but not to the same magnitude as observed in astronauts. The reduction in HLS animals is on the order of 6% and appears to be dependent upon the duration of the HLS. The majority of the literature reports the change in blood volume during HLS not to be significant (Bouzeghrane et al. 1996; Chew & Segal 1997; Tipton et al. 1998). A reduction in blood volume prior to hemorrhage drastically reduces survival and the success of resuscitation (Ho et al. 1996; Wade et al. 1992).

**Transcapillary fluid flux:** Spaceflight appears to redistribute fluid between body compartments in astronauts (Convertino 1996; Hargens & Watenpaugh 1996; Leach et al. 1996; Watenpaugh 2001). There is the decrease in the extracellular fluid volume comprised of a contraction of blood volume previously mentioned and a reduction in interstitial fluid volume. Simultaneously, intracellular fluid volume increases on the order of 10%. A major compensatory response to hemorrhage is the flux of fluid from the interstitial space into the vascular compartment (Hannon et al. 1990; Wade et al. 1992). In time there is movement from the intracellular space. This response is referred to as “auto-transfusion”. The lack of adequate movement from the intracellular compartment during hemorrhage would reduce survival. In the HLS model this has yet to be addressed.

**Fluid homeostasis**

The reduction in blood volume of astronauts during spaceflight suggests a new set-point for the maintenance of fluid homeostasis. The regulation of fluid balance in astronauts is altered with longer retention of a fluid load.
as a result of a reduced rate of urine excretion due to alteration in the response of regulatory hormones (Convertino 1996; Watenpaugh 2001). In the HLS rat model though blood volume is slightly reduced, fluid intake and urinary excretion are normal, suggesting a shifted fluid homeostasis similar to that observed in astronauts. This finding has led to the supposition that there is attenuation of the responses to changes in blood volume (Bouzeghrane et al. 1996; Deavers et al. 1980; Steffen et al. 1984; Tucker & Mendonca 1995). Upon return to Earth both astronauts and rats have a pronounced diuresis (Wade & Morey-Holton 1998; Wade et al. 2000). This increase in urine output is not immediately compensated for by an increase in fluid intake and results in hypovolemia. This response to landing, coupled with hemorrhagic hypovolemia, would put the patient at risk for a poor outcome. Thus, in the case of hypovolemic hypotension due to hemorrhage the compensatory responses may be attenuated in flight and after landing.

Endocrine System

Pressor hormones: In response to hemorrhage there is a progressive recruitment of pressor hormones. These hormones, norepinephrine, epinephrine, angiotensin II and vasopressin, increase peripheral resistance, leading to maintenance of blood pressure and blood flow to essential organs. In addition, the sympathetic hormones play a major role in substrate mobilization. Reports as to alteration of the sympathetic tone of astronauts are variable, appearing to be highly mission dependent (Leach et al. 1996, 1983; Macho et al. 1996; Stein & Wade 2001; Tipton et al. 1996). Changes in sympathetic tone and responsiveness are essential compensatory responses to hemorrhage. With HLS animals, as with astronauts, the reported plasma norepinephrine levels are variable (Hasser & Moffitt 2001). Furthermore, changes in sympathetic output in responses to manipulation are not definitive, but appear to be reduced. The renin-angiotensin system of astronauts is reduced (Leach et al. 1996, 1983). In addition, the response of this system as determined by response to fluid load was attenuated. In the HLS rodent plasma renin activity (PRA) decreased after 7 days of suspension (Bouzeghrane et al. 1996). However, no difference in PRA from control was noted after 14 days of acclimation to HLS.

Astronauts experience reduced vasopressin (Leach et al. 1996, 1983). In response to HLS the response of vasopressin in animals is variable. An acute increase in the rate of urinary excretion of vasopressin is found in response to HLS, however, 14 days of suspension produced no difference in plasma levels (Bouzeghrane et al. 1996). Alterations in astronauts and HLS rats of most of the pressor hormones occur during the period of acclimation with control values attained after a period of time. However, the alteration in responsiveness of the hormones to volume manipulations suggests compensatory changes due to hemorrhagic hypotension would be altered, contributing to an inadequate compensatory response.

Reproductive hormones: Spaceflight consistently reduces testosterone levels in astronauts and rats (Ortiz et al. 1999; Strollo 1999; Tou et al. 2002). The cause of this change is not well defined. There is no information as to the change of reproductive hormones in female astronauts (Ortiz et al. 1999; Strollo 1999; Tou et al. 2002). The level of reproductive hormones has been demonstrated to account for the pronounced gender differences in the response to hemorrhage (Jarrar et al. 2000; Remmers et al. 1998a; 1997, 1998b). A reduction in testosterone in male rats is beneficial in the presence of hemorrhage. The addition of estrogen contributes to an increase in survival. With the HLS model male rats have a significant reduction in plasma testosterone levels (Ortiz et al. 1999; Tou et al. 2002). In female rats HLS reduces estrogen and disrupts the reproductive cycle (Tou et al. 2005, 2004). Therefore, changes in reproductive hormones during spaceflight may be of benefit to male astronauts whose injuries result in hemorrhage, and a decrement in female astronauts.

Insulin/Glucagon: Investigations during spaceflight, in astronauts and rats, have demonstrated changes in glucose and insulin metabolism suggestive of a diabetic-like state (Macho et al. 1996; Stein et al. 2000; Tobin et al. 2002). There is an increase in circulating glucose and a reduction in insulin concentrations for the associated plasma glucose level (Macho et al. 1996). Furthermore, there appears to be a decrease in insulin sensitivity. Plasma glucagon levels are not changed. Hemorrhage decreases sensitivity to insulin in liver and muscle tissues (Carter 1998; Custalow et al. 2001). This leads to a catabolic state. Muscle atrophy and reduced insulin sensitivity as a result of spaceflight would theoretically adversely affect the normal compensatory response to hemorrhage. HLS rats exhibit enhanced sensitivity to insulin-induced glucose uptake when compared with normal control rats, and resistance to the actions of insulin when contrasted with rats similarly matched for the reduction in body mass gain (Mondon et al. 1992). Insulin binding is also reduced. A number of studies have produced conflicting results in this area (Koebel et al. 1993; Stump et al. 1992, 1993), but the ability to mobilize and transport glucose in response to hemorrhage is important to survival (Barton & Passingham 1982; Carter 1998; Chang et al. 2000; Ma et al. 2003). The diabetogenic state of space flight would adversely affect this compensatory response and alter outcome from hemorrhage.

Metabolic Changes

Negative energy balance: Astronauts experience a negative energy balance that is highly mission dependent and related to work load requirements (Stein 2000; Wade et al. 2002). Over the course of a Shuttle mission body mass is reduced (Sawin 1998; Stein 2000). A negative energy balance adversely impacts survival following hemorrhage (Nettelbladt et al. 1996). Bacterial translocation from the gut may also increase after a normally non-lethal hemorrhage if the patient is food deprived (Bark et al. 1995). A consistent finding in the HLS rat is a decrease in body mass on the order of 10%
(Morey-Holton & Globus 2002; Thomason & Booth 1990). Attempts to determine energy balance have been limited. We reported that food intake adjusted for body mass was similar for HLS and control rats (Wang & Wade 2000). Further, Blanc et al. (Blanc 2001, 2000) reported no change in energy expenditure during 7 days of suspension, and a net reduction in energy balance as intake was reduced. We have reported no change in the body mass of space flown rats (Wade et al. 2002). In this case the HLS model may be more representative of the astronaut than an animal on board the space craft.

**Substrate metabolism:** There are numerous reports of changes in substrate metabolism of astronauts and rats flown in space (Fitts et al. 2001; Stein 2000; Thomason, 1990). Many of the changes are associated with muscle disuse (Fitts et al. 2001; Picquet et al. 2000; Thomason & Booth 1990). There appears to be a preferential shift in large normally weight-bearing muscle from fat metabolism to glucose. In rats flown in space or HLS the changes in fiber type are similar to those observed in astronauts. This change in fiber type is associated with a reduction in the ability of the muscle to oxidize long-chain fatty acids, and an increased reliance on carbohydrate metabolism (Stein et al. 2000; Thomason & Booth 1990). In response to exercise these changes have led to a reduction in exercise performance due to limited metabolic reserves. Reliance on carbohydrates as a metabolic substrate is high in the presence of major hemorrhage (Boija et al. 1988; Custalow et al. 2001). Thus, increased reliance on this metabolic pathway for normal metabolism may limit the ability of this energy pool to serve as a reserve during hemorrhage. The end product of the use of carbohydrates in the presence of limited oxygen is lactate. Lactate increase is indicative of the magnitude of the oxygen debt incurred and is related to subsequent outcome (Wade et al. 1989). In the HLS model Fitts and colleagues (Fitts et al. 2001) have performed studies showing there is an increase in muscle glycogen, but in response to stimulation this reserve is rapidly used. Further, at rest there was an increase in tissue lactate that rapidly increased during stimulation. As blood flow is shunted away from muscle during hemorrhage the lack of shift in the metabolic substrate would lead to rapid depletion in energy reserves and a greater production of lactate and acidosis. These shifts in metabolism would have a negative impact on survival from hemorrhage and may preclude some commonly used resuscitation solutions.

Changes in liver metabolism during spaceflight will also influence responses to hemorrhage (Merrill et al. 1992; Stein et al. 1994). Flight alters a variety of metabolic pathways in liver tissue, reducing P-450 pathway enzymes and cholesterol biosynthesis. There appears to be a shift favoring gluconeogenesis as glycogen stores are increased. The liver is one of the first organs to show signs of injury during hemorrhage (Boija et al. 1988). The pathway changes during spaceflight may impact the ability of the liver to provide adequate substrate during hemorrhage, leading to a reduction in ATP stores. A reduction in liver ATP levels is associated with an increase in apoptosis after hemorrhagic hypotension (Mongan et al. 2002; Paxian et al. 2003). Alteration of substrate metabolism during spaceflight may adversely impact outcome following hemorrhagic hypotension due to traumatic injuries. The metabolic imbalance may persist during resuscitation as normal compensatory pathways diminish. The capability to stabilize the patient for an extended period of time following resuscitation is in jeopardy as well.

**Immune system:**
The immune system of astronauts and rats is dramatically altered during space flight (Sonnenfeld 2005b, 2005a, 2005c). The HLS model emulates many of the changes in the immune system reported during spaceflight. HLS has been used to assess possible countermeasures to immune dysfunction associated with space flight. The response of the immune system to hemorrhage plays a major role in outcome of the patient and subsequent morbidity. The dysfunction of this system could lead to a variety of differences in the response to hemorrhage and resuscitation.

**Environmental:**
The spaceflight environment is often thought of as only involving responses to microgravity. However, there are numerous other environmental factors that could adversely affect the ability of a patient to survive hemorrhage. A major environmental factor may be the transition from the microgravity to the normal gravity of Earth and the experience of hypergravity during landing. An example of the influence of the return to Earth’s gravity is the high incidence of astronauts experiencing orthostatic intolerance (Hargens & Waterpaugh 1996; Sawin 1998). Brizze and Walker (Brizze & Walker 1990) examined the response of reloading on blood pressure, heart rate and cardiac output following hind limb suspension for 7 days. They noted no difference in any of the measured hemodynamic parameters. With 10 minutes reloading, mean arterial pressure did not change, with trends towards an increase in heart rate and total peripheral resistance and a fall in cardiac output. Others have noted a significant reduction in blood pressure with reloading (Bayorh et al. 2002). These responses are similar to those observed in astronauts and do not bode well for an individual injured in space who is returned to Earth in a hypovolemic state.

**Response of the HLS Model to Hypotension:**
Studies of the HLS model response to hypotension are limited and only one examined the response to hemorrhage. Studies of hypotension have been directed at the baroreflex to assess the impact of return to the gravity of Earth on orthostatic intolerance, not the study of responses to hemorrhagic hypovolemia. In studies of the baroreflex the animals were administered a vasodilator at increasing doses. The heart rate response to a given fall in blood pressure provides an index of the responsiveness of the system. This compensatory response is mediated by the sympathetic nervous system. The response of heart
rate to administration of the vasodilator was not affected by HLS (Brizzee & Walker 1990; Hasser & Moffitt 2001; Moffitt et al. 1998). However, the response of sympathetic nerve activity decreased (Foley et al. 2005; Hasser & Moffitt 2001; Moffitt et al. 1998; Mueller et al. 2005; Mueller & Hasser 2003). The authors concluded that, as previously reported in astronauts (Hargens & Wartenpaugh 1996; Sawin 1998), HLS alters the arterial baroreflex, possibly contributing to orthostatic intolerance (Foley et al. 2005; Hasser & Moffitt 2001; Moffitt et al. 1998; Mueller et al. 2005; Mueller & Hasser 2003). The inability to increase sympathetic tone in response to a decrease in arterial pressure would also suggest a negative impact of HLS on the response to hemorrhage, adversely affecting outcome. The same authors have conducted preliminary experiments of the response to hemorrhage (Hasser & Moffitt 2001). The rats were exposed to HLS for 12 days. Mean arterial pressure, heart rate and sympathetic nerve activity were recorded. In response to HLS mean arterial pressure did not change, but heart rate increased. Rats were hemorrhaged at 3 ml/kg/min until attaining a mean arterial pressure of less than 40 mmHg. The amount of blood removed to reach the desired blood pressure was similar (control 20.2 ± 2.1 ml/kg and HLS 19.0 ± 1.8 ml/kg). However, the increase in sympathetic nerve activity in response to a reduction in pressure was attenuated in HLS animals. This preliminary work on hemorrhage, coupled with a body of literature that addresses the modification of the cardiovascular responsiveness of the HLS model, supports use of this method. Further, as the HLS model produces many of the metabolic, cardiovascular, immunologic and endocrine changes observed in astronauts during spaceflight we propose it as an appropriate means for the initial evaluation of resuscitation procedures to be used to treat hemorrhagic hypovolemia in astronauts.

Hemorrhage Models:
As noted previously, the traumatic injuries that may induce loss of blood volume necessitating fluid replacement in an astronaut are quite diverse. Fortunately, a number of experimental hemorrhage models can mimic a range of clinical scenarios, such as fixed pressure, fixed volume, uncontrolled and crush hemorrhage models. The first model, fixed pressure, is one of the most common. This method developed by Wiggers and colleagues bleeds the animal to a fixed pressure and sustains that pressure by removal of additional blood or replacement of the shed blood volume (Wiggers 1950). This model contributed to the hypothesis of irreversible hemorrhage in that at some point, no matter what resuscitation interventions are used, survival is not possible (Shah et al. 1998). This model provides insights into cardiovascular compensation and other endogenous factors mediating restitution. The second is the fixed volume hemorrhage model with the set removal of volume of blood per kilogram of body mass (Hannon et al. 1990; Shah et al. 1998). This approach allows differences between initial conditions to be assessed. It also allows the condition of the animal to be evaluated in terms of the net response to hypervolemia. We have used this approach with a slight modification, extending the period of bleeding at a slower rate to mimic the drop in the drive pressure observed clinically. The third model is of uncontrolled hemorrhage to simulate a major injury in which the control of bleeding is not easily attained (Bickell et al. 1991, 1989, 1994; Krausz et al. 2000). This simulates major traumatic injuries to the torso. The model has been used extensively to assess initial resuscitation in the pre-hospital setting. The fourth model includes major tissue damage in the presence of a fixed volume of bleeding (Jarrar et al. 2000; Remmers et al. 1998a., 1997, 1998b). This model allows the study of responses to tissue injury which modifies compensatory adjustment. In evaluating approaches to resuscitation the use of a number of the animal models of hemorrhage is highly recommended (Fluid Resuscitation:State of the Science for Treating Combat Casualties and Civilian Injuries. 1999). Although there are other approaches to the study of hemorrhage however, the above methods are widely used to assess the efficacy of resuscitation procedures. We have deliberately not addressed burn or septic shock. However, these forms of hypovolemic shock would also be modified by acclimation to the spaceflight environment and should be evaluated.

Resuscitation Parameters:
The approach to resuscitation following traumatic injuries and the appropriate endpoints are controversial. Recent studies using physiological endpoints have been effective in increasing survival and reducing morbidity. However, they require extensive physiological monitoring and staffing. Thus, they have not been used outside the hospital. This has led to the approach of stabilizing the patient until definitive care can be administered, which would be the optimal situation in the spaceflight environment. These methods include delayed fluid administration, hypotensive resuscitation, modifications of the fluids administered and mechanisms for lowering metabolism (Fluid Resuscitation:State of the Science for Treating Combat Casualties and Civilian Injuries. 1999; Bickell et al. 1994; Dutton et al. 2002; Knudson et al. 2003; Kramer 2003).

Another area of controversy is the endpoint for evaluation of resuscitation efficacy (Fluid Resuscitation: State of the Science for Treating Combat Casualties and Civilian Injuries. 1999; Revell et al. 2003; Rhee et al. 1998; Shoemaker et al. 1996; Wade & Holcomb 2005; Zhao et al. 2002). The ultimate endpoint is survival. However, these studies are expensive and involve large numbers of subjects and thus are not appropriate for the initial assessment of an intervention. Later in the development of a process they are necessary. Many have felt that restoration of blood volume and cardiovascular function are adequate indices of resuscitation. This is not always true. For example, the use of crystalloids may replace blood volume and improve cardiac output in the short term. However, due to hemodilution, oxygen delivery is reduced, leading to death. Therefore, long-term survival must be assessed. This is especially true in the spaceflight environment where the extraction of the patient will be days, if not weeks, and the acclimation process may...
necessitate alteration of the standard of care approaches to resuscitation.

SUMMARY
The question is not if a traumatic injury requiring resuscitation during spaceflight will occur, but what systems and clinical guidelines will be in place to handle it when it does occur, without loss of life or compromise of the mission. The need for the care of traumatic injuries has been recognized by the space agencies. Extensive efforts and resources have been expended to meet these contingencies by applying successful Earth-based clinical practices. However, acclimation to the spaceflight environment results in alterations in the cardiovascular, endocrine, immune, and hemopoietic systems as well as metabolic changes. These changes will drastically alter the response of the patient to injury. These alterations have to be considered in clinical guidelines to care for the injured space traveler, and must be validated on the ground and in flight in clinically relevant animal models.

REFERENCES


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