

REPORT DOCUMENTATION PAGE			<i>Form Approved</i> OMB No. 0704-0188		
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1. REPORT DATE (DD-MM-YYYY) 31-08-2010		2. REPORT TYPE Dissertation		3. DATES COVERED (From – To) August 2007 – August 2010	
4. TITLE AND SUBTITLE Secondary Insults of Traumatic Brain Injury in CCATT Patients Returning from Iraq/Afghanistan: 2001-2006			5a. CONTRACT NUMBER		
			5b. GRANT NUMBER		
			5c. PROGRAM ELEMENT NUMBER		
6. AUTHOR(S) Susan F. Dukas			5d. PROJECT NUMBER		
			5e. TASK NUMBER		
			5f. WORK UNIT NUMBER		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) USAF School of Aerospace Medicine Department of Aeromedical Research (FHC) 2510 Fifth St. Wright-Patterson AFB, OH 45433-7913			8. PERFORMING ORGANIZATION REPORT NUMBER AFRL-SA-WP-OT-2011-0008		
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)			10. SPONSORING/MONITOR'S ACRONYM(S)		
			11. SPONSOR/MONITOR'S REPORT NUMBER(S)		
12. DISTRIBUTION / AVAILABILITY STATEMENT Distribution Statement A: Approved for public release; distribution is unlimited. Case Number: 88ABW-2011-5333, 5 Oct 2011					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Traumatic brain injury (TBI) patients are highly susceptible to secondary insults to the injured brain (e.g., hypoxia, hypotension, hyperthermia, hypothermia, and hyperglycemia). Patients with secondary insults have been shown to have worse outcomes. Over one-third of the patients transported by Critical Care Air Transport Teams (CCATTs) have had TBIs. Considering CCATT patients travel thousands of miles, pass through multiple hospital systems, and are exposed to the stresses of flight on military cargo aircraft, the occurrence and timing of secondary insults need to be explored. This study describes the occurrence of secondary insults in isolated TBI patients transported by CCATTs from the point of injury to arrival in the U.S. between 2001 and 2006. A descriptive retrospective cohort design was used to conduct a secondary analysis of 64 CCATT patients with isolated TBI from the Wartime Critical Care Air Transport Database. The median days from the point of injury to patients arriving in Germany and in the U.S. decreased from 2.5 to 1 day and 8 to 3.5 days, respectively. Over half of the study participants had at least one documented episode of a secondary insult. Hyperthermia was the most common secondary insult, with the occurrence rate increasing from the point of injury to arrival in the U.S. No significant difference in the documented occurrence of secondary insults was found between type of aircraft used for CCATT transport, even with a change in primary aircraft. Finally, no significant difference in the documented occurrence of secondary insults was found by year of occurrence. Despite the limitations of missing data, secondary insults were common and should be targeted for prevention to optimize outcomes. The use of opportune cargo aircraft by CCATTs to transport patients is supported. The decision to transport patients earlier before they are stabilized is also supported. Additional studies with more complete data and detailed outcome measures are warranted.					
15. SUBJECT TERMS Traumatic brain injury, critical care air transport, secondary insults, hypoxia, aeromedical evacuation					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			Lt Col Susan F. Dukas
U	U	U	SAR	139	19b. TELEPHONE NUMBER (include area code)

Secondary Insults of Traumatic Brain Injury in CCATT Patients
Returning from Iraq/Afghanistan: 2001-2006

by
Susan Fae Dukes

Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2010

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Dedication

This work is dedicated to my peers who have **lived** these experiences with me, to my friends who have **laughed** with me through thick and thin, to my family who have **loved** me through it all, and to my teachers and mentors through whom I have **learned** so much. I thank my God for you all.

Acknowledgements

A very special thank you to my dissertation committee members who each contributed in a very unique way to the completion of this project:

Dr. Meg Johantgen – my advisor and committee chair, whose guidance and expertise kept me grounded and on track

Dr. Tricia Morton – my Master’s Degree advisor, whose critical care expertise and editorial skills have been priceless

Dr. Erika Freidmann – my teacher and statistician, whose understanding of statistical analysis far surpassed what was appropriate for this project

Dr. George Zangaro – my teacher and military confidant, whose insight, understanding, and reassurance was highly valued

Dr. Liz Bridges – my Air Force expert and mentor, whose original data made this project possible and steady encouragement finally paid off!

Abstract

Background: Traumatic brain injury (TBI) patients are highly susceptible to secondary insults to the injured brain (e.g., hypoxia, hypotension, hyperthermia, hypothermia, and hyperglycemia). Patients with secondary insults have been shown to have worse outcomes. Over one third of the patients transported by Critical Care Air Transport Teams (CCATT) have had TBIs. Considering CCATT patients travel thousands of miles, pass through multiple hospital systems, and are exposed to the stresses of flight on military cargo aircraft, the occurrence and timing of secondary insults need to be explored.

Purpose: This study describes the occurrence of secondary insults in isolated TBI patients transported by CCATTs from the point of injury to arrival in the United States between 2001 and 2006.

Methods: A descriptive retrospective cohort design was used to conduct a secondary analysis of 64 CCATT patients with isolated TBI from the Wartime Critical Care Air Transport Database. Data elements in the database were abstracted from existing records including theater evacuation and trauma registry systems, transport documents, flow sheets, and hospital medical records.

Results: The median days from the point of injury to patients arriving in Germany and in the United States decreased from 2.5 to 1 day and 8 to 3.5 days respectively. Over half of the study participants had at least one documented episode of a secondary insult. Hyperthermia was the most common secondary insult with the occurrence rate increasing from the point of injury to arrival in the United States. No significant difference in the documented occurrence of secondary insults was found between type of aircraft used for CCATT transport even with a change in primary aircraft. Finally, no significant difference in the documented occurrence of secondary insults was found by year of occurrence.

Conclusion: Despite the limitations of missing data, secondary insults were common and should be targeted for prevention to optimize outcomes. The use of opportune cargo aircraft by CCATTs to transport patients is supported. The decision to transport patients earlier before they are stabilized is also supported. Additional studies with more complete data and detailed outcome measures are warranted.

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List of Abbreviations

AOR	Military area of responsibility
bTBI	Traumatic brain injury from an explosive blast
CCATT	Critical Care Air Transport Teams
CONUS	Contiguous United States
CPP	Cerebral perfusion pressure
CSF	Cerebral spinal fluid
cTBI	Closed head traumatic brain injury
DAI	Diffuse axonal injury
DRS	Disability Rating Scale
DUA	Data Use Agreement
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
GOSE	Expanded Glasgow Outcome Scale
ICP	Intracranial Pressure
ICU	Intensive care unit
IRB	Institutional Review Board
ISS	Injury Severity Score
JTTS	Joint Theater Trauma System
LOC	Loss of consciousness
LOS	Length of stay
LRMC	Landstuhl Regional Medical Center
MTF	Medical treatment facility
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
pTBI	Penetrating traumatic brain injury
PTSD	Post traumatic stress disorder
SBP	Systolic blood pressure
SpO ₂	Oxygen saturation
TBI	Traumatic brain injury
TRAC ² ES	U.S. Transportation Command and Control Evacuation System
USAF	United States Air Force
WCCATD	Wartime Critical Care Air Transport Database

Chapter 1: Introduction

1.1 Background

Traumatic brain injury (TBI) remains a leading health problem around the world. TBI patients who survive the primary trauma are highly susceptible to secondary insults to the injured brain. These secondary insults are a delayed, physiologic response to the primary injury (Hickey & Prator, 2009). Patients with secondary brain injury have been shown to have worse outcomes. Over one third of the patients transported by Critical Care Air Transport Teams (CCATT) since the start of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) in Afghanistan have had TBIs (Bridges & Evers, 2009). CCATT patients travel thousands of miles, pass through multiple hospital systems, and are exposed to the stresses of flight lasting often as long as 8 to 14 hours in the austere environment of military cargo aircraft (Richardson, 2007).

In OIF/OEF, explosive blast is by far the most common wounding etiology earning mild TBI the title of the “signature injury” of the current conflict in Iraq (Hoge, McGurk, Thomas, Cox, Engel & Castro, 2008). From this growing pool of clinical experience, TBI from an explosive blast (bTBI) is becoming recognized as a disease distinct from penetrating TBI (pTBI) and blunt or closed head TBI (cTBI) (Ling, Bandak, Armonda, Grant & Ecklund, 2009). Explosions produce a wide variety of injuries by multiple mechanisms in many different body parts. Therefore, the picture of the OIF/OEF critically injured casualty is quite complex making it difficult to isolate effects of individual injuries (Champion, Holcomb & young, 2009). One way to isolate effects is by studying patients with isolated traumatic brain injuries.

1.2 Statement of the Problem

No research studies have been found that examine the effects of secondary insults on TBI in wartime casualties. Some of the questions that drove the development of this study include:

- a. Is there a difference in secondary insults during different stages of transport from the battlefield to the United States?
- b. Is there a difference in secondary insults by the type of aircraft used for transport?
- c. Is there a difference in secondary insults by the etiology of injury?
- d. Is there a best time to transport patients?

Many of the secondary insults of TBI can only be diagnosed or assessed using sophisticated equipment in a hospital environment. Therefore, the secondary insults most commonly assessed in the military transport environment include: hypoxia, hypotension, hyperthermia, hypothermia, and hyperglycemia.

1.3 Purpose

In an effort to answer the questions above, the following specific aims were developed:

1. Describe the occurrence of secondary insults (hypoxia, hypotension, hyperthermia, hypothermia, and hyperglycemia) in isolated TBI patients transported by CCATTs.
2. Determine if occurrence of secondary insults in isolated TBI CCATT patients is associated with extent of injury (Injury Severity Score), etiology of TBI (blast vs. non-blast), type of aircraft used for transport (C-17 vs. C-141), and year of occurrence (from beginning of OIF/OEF to most recent available data).

A better understanding of secondary insults in TBI CCATT patients can help guide preventive measures thus contributing to maximized outcomes in military members injured while serving our country. The lessons learned here, however, can also be applied to civilian TBI patients in austere environments or those enduring long transports.

1.4 Conceptual Model

The conceptualization for this study is one of a physiologic model adapted from Dietrich (2000). This severe TBI framework begins with the primary injury which can be followed by complications from secondary injury. These secondary injuries can be either or both complicating processes initiated at injury or secondary insults which are later causes that can precipitate additional insult to the injured brain. All of these processes can affect the patient's outcome. This study focused on secondary insults and different variables found within the environment of the CCATT TBI casualty. It is not possible to examine all aspects of secondary insults or even all variables impacting a select number of secondary insults. Therefore, the secondary insults and variables addressed in this study are depicted in the conceptual model found in Figure 1-1.

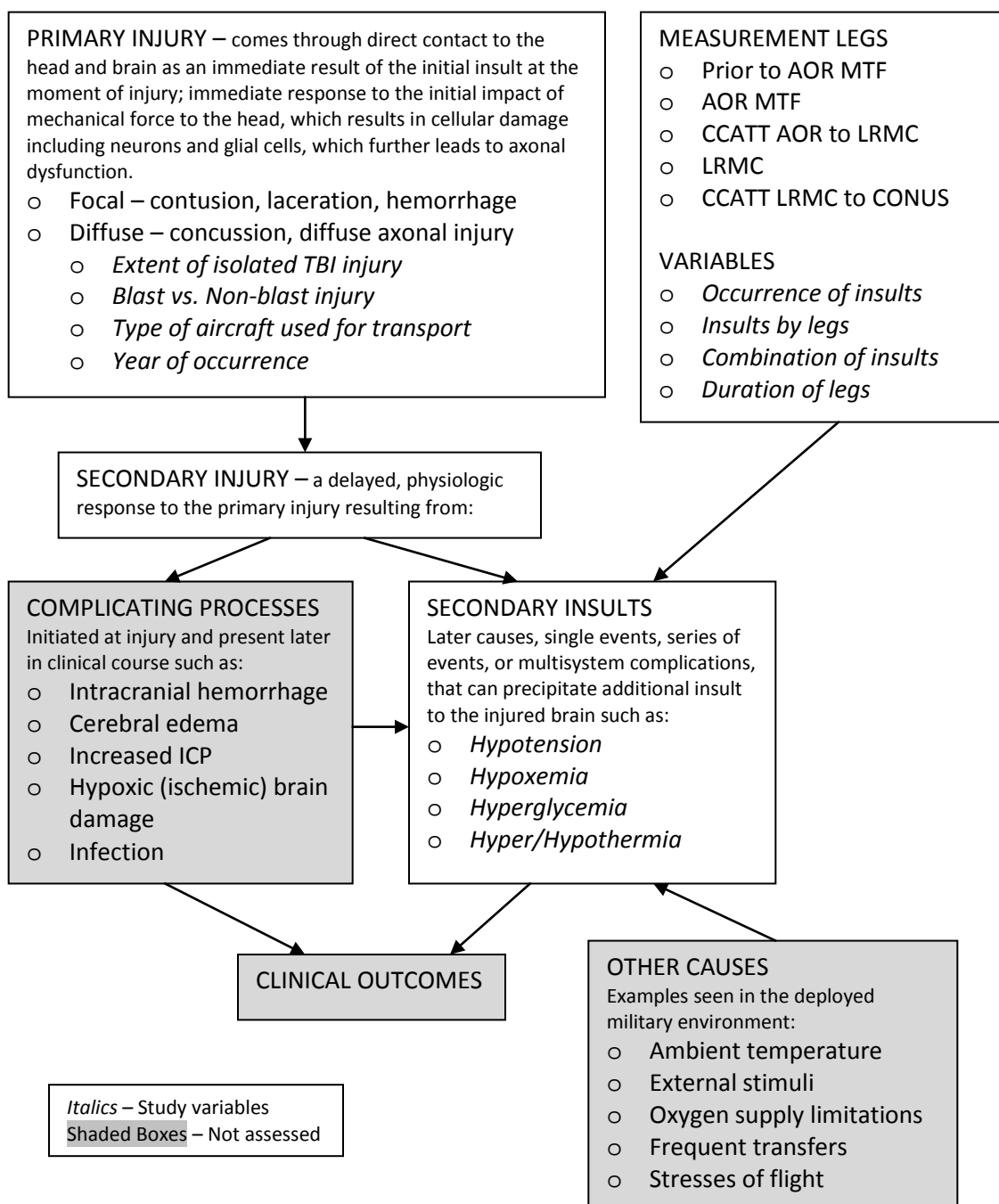


Figure 1-1. Conceptual Model

TBI – Traumatic Brain Injury; ICP – Intracranial Pressure; AOR – military Area of Responsibility; MTF – Medical Treatment Facility; CCATT – Critical Care Air Transport Team; LPMC – Landstuhl Regional Medical Center; CONUS – Contiguous United States

Adapted from Dietrich, W. D., 2000. Trauma of the nervous system. In Bradley, W., Daroff, R., Fenichel, G. & Marsen, C. (Eds.). *Neurology in clinical practice*, 3rd ed. Boston: Butterworth & Heinemann.

Chapter 2: Review of the Literature

2.1 Overview

Traumatic brain injury is a leading health concern around the world and has been designated the signature injury of OIF/OEF (Hoge, McGurk, Thomas, Cox, Engel & Castro, 2008). Many studies have been conducted with civilian TBI patients exploring secondary insults encountered and resulting outcomes. Many similarities exist between civilian and military TBI casualties but many differences also exist. Some of the biggest differences are the environment in which military TBIs occur, the explosive blasts causing many of the injuries, and the prolonged transport process encountered in returning these patients back to the United States.

Following a brief review of the characteristics of TBI including TBI from explosive blasts, the literature summarizing the occurrence and outcomes of the secondary insults examined in this study is discussed. This discussion is followed by a review of the impact of flight as it affects the TBI patient.

2.2 Characteristics of TBI

Traumatic brain injury (TBI) is an injury to the skull, brain, or both of sufficient magnitude to interfere with normal function and requires treatment (Hickey & Prator, 2009). In the United States alone, there are 1.5 million new cases of TBI each year of which close to one-quarter million will require hospitalization, 50,000 will die, and over 80,000 people will live with long-term disabilities (Thurman, Alverson, Dunn, Guerrero & Sniezek, 1999). Since the start of Operation Enduring Freedom in Afghanistan (OEF) and Operation Iraqi Freedom (OIF), nearly 17,000 U.S. wounded and injured casualties have required medical air transport from Iraq (Iraq Coalition Casualty Count, 2008). Of

these, over 2,700 have been intensive care patients requiring transport by Critical Care Air Transport Teams (CCATT) of which over one third have had TBIs. In OEF/OIF, explosive blast is by far the most common wounding etiology earning mild TBI the title of the “signature injury” of the current conflict in Iraq (Hoge, McGurk, Thomas, Cox, Engel & Castro, 2008). In a descriptive analysis of 433 casualties with TBI, mild TBI accounted for less than half the sample whereas moderate and severe TBIs accounted for 56% of the sample. Twelve percent of the sample had penetrating brain injury and closed TBI accounted for 88% of the group demonstrating closed brain injury as a mechanism of injury is more common in OEF/OIF (Warden, 2006).

2.2.1 Brain Injury Classification

Brain injuries can be classified as focal or diffuse (see Figure 2-1). Focal brain injuries include contusion, laceration, and hemorrhage. Hemorrhage is further divided into epidural hematoma, subdural hematoma, and intracerebral hematoma. Diffuse brain injuries include concussion and diffuse axonal injury (DAI).

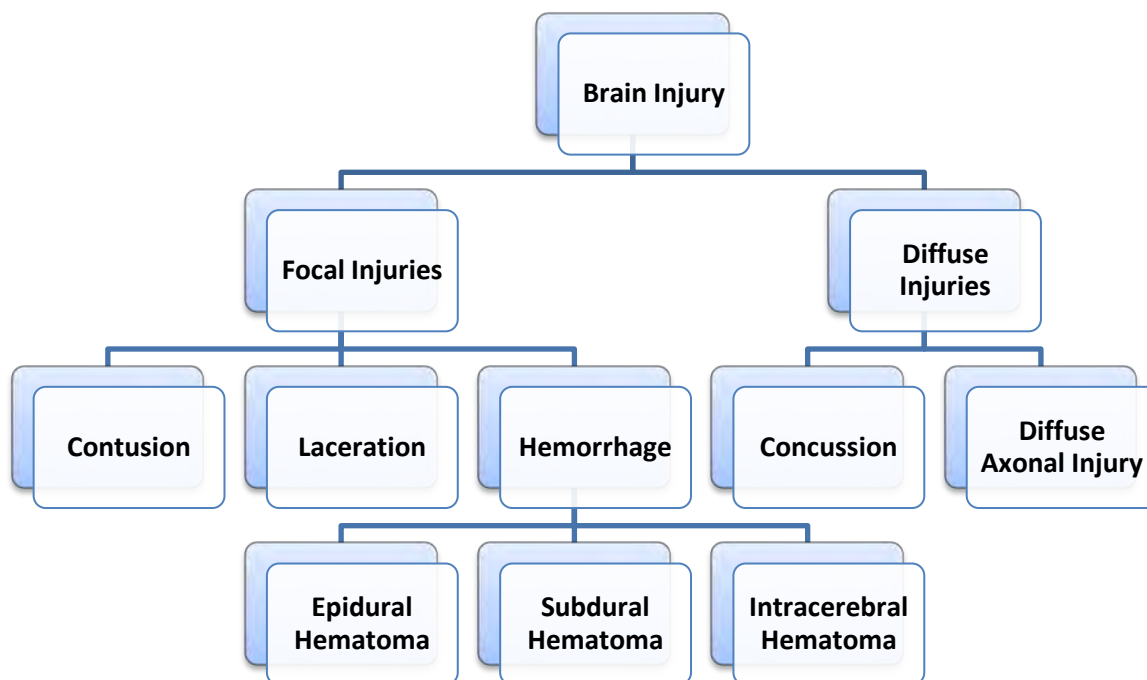


Figure 2-1 Classification of Brain Injury

Adapted from Hickey, J. & Prator, B. (2009). Craniocerebral injuries. In Hickey, J. *The clinical practice of neurological and neurosurgical nursing*, (6th ed., p. 371). Philadelphia: Lippincott Williams & Wilkins.

2.2.2 Mechanism of Injury

The mechanism of injury is the event that caused the injury. Traditionally, patients with TBI are injured from either a blunt or penetrating mechanism or a combination of the two. Because of the ongoing involvement in OEF/OIF, there are increasing numbers of patients encountering TBI caused by an explosive blast (bTBI). From this growing pool of clinical experience, bTBI is becoming recognized as a disease distinct from penetrating TBI (pTBI) and blunt or closed head TBI (cTBI) (Ling, Bandak, Armonda, Grant & Ecklund, 2009).

2.2.2.1 Penetrating TBI

When a penetrating TBI occurs, a foreign object enters the bony skull and travels through the brain parenchyma. When a penetrating TBI happens, neurons, glia, and fiber

tracts are physically disrupted which are further exacerbated by ischemia and hemorrhage. Signs and symptoms include an altered level of consciousness and are dependent on the parenchyma injured by the foreign body tract of travel. The seriousness of the clinical impairment may greatly exceed what one might expect from the size of the object if the object travels at very high speed such as a rifle bullet. Cavitation of brain tissue as a result of the high speed object causes the increased impairment. The surface lesion where the foreign body entered is characteristic of pTBI. There may also be another skull lesion where the foreign body exited. CSF and brain tissue can often be observed at the areas of skull defect. Hemorrhage, cerebral edema, and mangled tissue are all classic signs of pTBI (Dietrich & Bramlett, 2008; Ling, Bandak, Armonda, Grant & Ecklund, 2009).

2.2.2.2 Closed Head TBI

In a blunt or cTBI, the brain function is disrupted by brain motion and deformation within the cranium resulting in injuries to the brain parenchyma, blood vessels, and fiber tracts. The severity of the mechanical insult the brain experiences determines the patient's clinical presentation. Deceleration forces result in injuries when an individual's head strikes an immovable object whereas acceleration forces produce injuries when a moving object strikes an individual's head. Acceleration-deceleration forces produce injuries in combination since rapid changes in velocity produce rapid changes in the velocity of the brain in the cranial vault. Rotational forces produce side-to-side and twisting motions of the brain within the cranial vault. These injuries often occur together with acceleration-deceleration injuries and result in tension and shearing of the brain tissue. Deformation forces are usually the result of direct blows to the head

that change the shape of the skull and compress brain tissue. The speed of the impact determines the extent of the damage and the resulting injury (Blank-Reid, McClelland & Santora, 2008).

2.2.2.3 Explosive Blast TBI

To understand how an explosive blast can inflict TBI, it is necessary to have a basic understanding of the chain of blast injuries. It is also helpful to understand how injuries differ whether the explosion occurs in an open or enclosed space. Finally, a discussion of the characteristics of bTBI and their similarities and differences with pTBI and cTBI will help present a clear understanding of bTBI.

There are five layers or types of blast injuries. These include primary injuries, secondary injuries, tertiary injuries, quaternary injuries, and quinary injuries (DoD Directive, 2006). Blast victims may have any or all layers of injury. Secondary injuries are the most common.

Detonation of an explosive device sets off a chain of interactions. A shock pressure wave radiates from the explosion. Immediately after the explosion, there is an acute increase in pressure followed by a longer period of negative pressure. The increase in pressure causes primary blast injuries and the negative pressure displaces organs and causes secondary soft tissue trauma by sucking debris into the void. The blast wave causes injuries to gas filled organs such as the eardrums, lungs, and intestinal wall which are at particular risk. The pressure wave can also cause an implosion of gas bubbles followed by acute expansion after the blast wave passes. The implosion and rapid gas expansion causes tissue injury resulting from the mini-explosions and also may force air into surrounding tissues and blood vessels, which increases the risk for an acute gas

embolism. Finally, as the blast wave passes through the body, it may cause acceleration and the displacement of viscera and other organs and tissues (Bridges, 2006). Primary blast injuries to the brain include concussion and barotrauma caused by acute gas embolism (DePalma, Burris, Champion & Hodgson, 2005).

Explosive devices often contain metallic and other fragments designed to cause penetrating wounds. Secondary blast injuries are a result of the blast wind propelling explosion fragments and displaced debris creating multiple penetrating injuries. Even though these are termed secondary injuries, fragments are usually the predominant wounding agent and the leading cause of death in both military and civilian terrorist attacks (Champion, Holcomb & Young, 2009; DePalma, Burris, Champion & Hodgson, 2005).

Blast wind also propels people onto hard surfaces creating blunt or tertiary injuries. Blast winds can be strong enough to tumble a victim across the ground leading to abrasions and contusions, or cause blunt trauma from being thrown against a structure. A blast wind may also have enough force to cause fractures, traumatic amputations, and open and closed brain injuries (Bridges, 2006; DePalma, Burris, Champion & Hodgson, 2005). This classification also includes crush injuries caused by structural collapse. Structural collapse lead to crush injuries and extensive blunt trauma, whereas penetrating trauma is caused by flying fragments.

Quaternary blast injuries are those explosion-related injuries, illnesses, and diseases not due to primary, secondary, or tertiary injuries. They encompass exacerbations or complications of persisting conditions. Burns, inhalation injury, and asphyxiation from heat, flames, gas, and smoke created during the explosion are also

considered quaternary injuries (DePalma, Burris, Champion & Hodgson, 2005). Finally, quinary blast injuries are produced when bacteria or radiation are added to the explosive device and are released on detonation (DoD Directive, 2006).

Even though most explosions in Iraq and Afghanistan occur in open spaces, it is important to note that explosive effects are substantially different in closed spaces. If an explosion occurs inside a closed space, a casualty is more likely to have a primary blast injury due to the amplified overpressure from a reflected blast wave (Bridges, 2006).

Closed spaces cause blast waves to be deflected, ricochet, and coalesce. Their destructive power is magnified in closed spaces and large numbers of secondary fragments are generated through the breakup of structures and vehicles (Champion, Holcomb & Young, 2009). In closed spaces, each explosive blast must be analyzed individually since the confined space will result in different wave patterns unlike explosive blasts in open field conditions (Ling, Bandak, Armonda, Grant & Ecklund, 2009). Individuals close by each other in a closed space when an explosion occurs can sustain very different injury severity depending on the exposure to the deflecting blast waves (Warden, 2006).

Primary blast overpressure injuries, in general, are relatively uncommon. Most explosion related injuries are caused by fragments propelled over a far greater radius and often combined with tertiary blast injuries. This difference in definitions can lead to confusion since the term “blast injury” has become a general descriptor of injuries from explosion. The use of this term, however, disguises the fact that most injuries are caused by multiple mechanisms, predominately from penetrating fragments and not by blast overpressure (Champion, Holcomb & Young, 2009).

Additional uncertainty exists in regards to the precise causes and mechanisms of primary bTBI. The action generated by the explosive blast and the way the explosive blast interacts with the body to produce injury are areas requiring further study. For bTBI, it is likely that more than one primary injury mechanism exist. The assumption is that high pressures lead to air-filled organ failure. This assumption would lead to the expectation of a high prevalence of blast lung injury. Clinical experience from OEF/OIF, however, shows that blast lung injury occurs infrequently, acute respiratory distress syndrome is reported only in conjunction with other severe injuries, and the bowel has not been found to be injured by explosive blasts unless there is shrapnel penetration (Ling, Bandak, Armonda, Grant, & Ecklund, 2009). In contrast, bTBI is much more common and since the brain is not an air-filled organ, other mechanisms must be responsible such as those from shock wave effects (Ling, Bandak, Armonda, Grant, & Ecklund, 2009). A possible explanation for this difference is that interceptor body armor may be protecting the lungs and bowel from blast forces. Another possible explanation is that other physical forces may contribute to explosive blast injury. Explosive detonation in addition to pressure waves release light, acoustic, thermal, and electromagnetic energies. Some of these, in addition to toxic fumes, can be injurious to the central nervous system. The affect of these forces on bTBI are unknown and evidence is lacking as to whether they can be included or excluded as potential causes of bTBI (Ling, Bandak, Armonda, Grant, & Ecklund, 2009).

Blast TBI shares clinical features of both pTBI and cTBI. The mechanical forces from secondary and tertiary injuries present as penetrating and closed head injuries as a result of propelled fragments, tumbling or falls, and collapsing buildings. The effects of

a simultaneous exposure to the primary blast, however, are not well understood.

Additionally, we know very little about the possible side effects of exposure to multiple blasts when a person is exposed to a blast but does not require medical evacuation from the war zone (Warden, 2006).

Neurosurgeons and neurointensivists caring for casualties of explosive blast victims from OEF/OIF have observed that the frequency, intensity, and duration of the pathophysiological characteristics of bTBI are different than those of civilian brain injuries. The main unique characteristics noted are edema, vasospasm, and intracranial hemorrhage (Bauman et al., 2009). The diffuse cerebral edema and hyperemia seen in severe bTBI develops rapidly, often within an hour after the blast injury. When a subarachnoid hemorrhage occurs, it indicates a more severe injury and is often accompanied by severe brain edema, hyperemia, and delayed vasospasm. The delayed vasospasm is thought to be the cause of delayed neurological deterioration but can develop early, often within 48 hours of injury (Armonda et al., 2006). This clinical presentation appears to be more common following blast than other types of TBI and has resulted in decompressive craniectomies being performed more commonly than for pTBI or cTBI (Schlifka, 2007).

Any comparison of bTBI with pTBI and cTBI would not be complete without discussing the development of post traumatic stress disorder (PTSD) following TBI. Studies suggest that those with mild TBI are at greater risk for developing PTSD than patients with severe brain injuries (Klein, Caspi & Gil, 2003). In addition, symptoms of PTSD have been reported more often in individuals injured by blast than in those who received their TBI from other mechanisms (Warden, 2006). Much care needs to be

exercised when diagnosing and treating these patients since bTBI and PTSD can occur alone or together and may be difficult to differentiate (Hoge et al., 2008; Ling, Bandak, Armonda, Grant & Ecklund, 2009).

Because of the unknowns surrounding the mechanisms of injury for blast injuries, mechanism of injury was separated into those injuries caused by a blast injury and those injuries not caused by a blast injury. This separation will help begin to build a body of knowledge targeting blast injuries in military casualties.

2.2.3 Isolated TBI vs. TBI with Polytrauma

The picture of the OIF/OEF critically injured casualty is quite complex making it difficult to isolate effects of individual injuries. Explosions produce a wide variety of injuries by multiple mechanisms in many different body parts. Common injuries in blast-related polytrauma include open wounds; traumatic amputations; and injuries to the brain, spinal cord, eye and musculoskeletal system, as well as psychiatric problems. There is no other wounding agent as effective at inflicting such a wide variety of injuries (Champion, Holcomb & Young, 2009; DePalma, Burris, Champion & Hodgson, 2005; Scott, Belanger, Vanderploeg, Massengale & Scholten, 2006).

bTBI in the context of polytrauma is an emerging medical concern in the military. bTBI is often accompanied by hemorrhagic blood loss and systemic injury. This is particularly a concern since laboratory studies suggest that TBI adversely affects cardiovascular homeostatic responses to blood loss and resuscitation (Long, Bentley, Wessner, Cerone, Sweeney & Bauman, 2009; McMahon, Kenny, Bennett & Kirkman, 2008). It has also been suggested that bTBI substantially alters fluid resuscitation requirements. This altered fluid requirement is especially the case when the bTBI occurs

in combination with detrimental effects on other organ systems. As a result, resuscitation requirements may be much different for these blast casualties (Long, Bentley, Wessner, Cerone, Sweeney & Bauman, 2009).

With the complexity of wartime injuries, it is difficult to isolate the effects of bTBI. This can be done, however, in two ways; first by using patients with isolated bTBI and secondly by the use of injury models in a laboratory setting depending on the intent of the study. bTBI is a predominant cause of neurotrauma in OIF/OEF and its etiology is largely undefined. Laboratory models can be used to help understand the physiological, neuropathological, and neurobehavioral consequences of blast exposure whereas clinical epidemiologic studies would be able to examine the effects of bTBI by sampling patients with isolated bTBI.

Military-relevant injury models have been developed recently. The penetrating ballistic brain injury model and a blast injury model are two of significance to TBI (Dietrich & Bramlett, 2008). The penetrating brain injury model mimics a bullet wound by expanding and contracting a balloon that has been inserted into the brain. Injury severity and placement of the probe can be varied so that different types of bullet injuries can be studied. Blast injury models mimic whole-body blast or local blast injury. Compression-driven shock tubes are used to simulate blast effects whereas explosive models include thermal energy from the fireball, differentially powerful frequencies, and electromagnetic pulses. Neither of these models accounts for multi-phase flow. Models simulating humvee and building conditions generate complex pressure waveforms found when an explosion is detonated in a walled structure. Most of these laboratory studies

utilize rats but some also use a swine model (Bauman et al., 2009; Long, Bentley, Wessner, Cerone, Sweeney & Bauman, 2009).

Any attempts at this time to try and isolate the effects of bTBI in a polytrauma patient would be met with great difficulty. First of all, bTBI signs and symptoms are still not well understood and defined and secondly, serious injuries beyond TBI such as traumatic limb amputation and hemorrhagic shock require aggressive resuscitation and other systemic therapies making it nearly impossible to isolate the effects of the bTBI in a clinical environment.

2.2.4 Severity of TBI

Clinically, TBI severity is often classified according to the Glasgow Coma Scale (GCS) (see Table 2-1). Mild TBI patients have GCS scores of 14-15, moderate brain injury has GCS scores of 9-13, and severe brain injury is defined by GCS scores of 3-8 (Dietrich & Bramlett, 2008; Hickey & Prator, 2009). Some have advocated the motor component of the GCS should be used instead of the whole GCS since it contains all the information of the GCS and can be measured in intubated patients (Healey, et al., 2003). In civilian practice, concussion, a form of TBI, uses different criteria (see Table 2-2). A person with a mild concussion experiences confusion lasting less than 15 minutes but no loss of consciousness. Moderate concussion symptoms include confusion lasting longer than 15 minutes but no loss of consciousness, whereas a person with a severe concussion experiences a loss of consciousness (Dietrich & Bramlett, 2008; Ling, Bandak, Armonda, Grant & Ecklund, 2009). The military medical community, however, is recognizing a need for developing severity grading criteria that is appropriate for TBI injuries as a result of explosive blasts (see Table 2-3). Mild blast TBI would be defined as a loss of

consciousness less than 1 hour and post-traumatic amnesia less than 24 hours after exposure to an explosive blast. Moderate blast TBI would encompass a loss of consciousness greater than 1 hour but less than 24 hours and amnesia greater than 1 day but less than 7 days. Casualties with severe blast TBI would experience a loss of consciousness greater than 24 hours and amnesia greater than 7 days (Ling, Bandak, Armonda, Grant & Ecklund, 2009). This blast TBI classification is still in the proposal stages and has not yet been adapted by the medical community.

Table 2-1 Civilian TBI Classification

Mild	Moderate	Severe
<ul style="list-style-type: none"> • GCS: 14-15 	<ul style="list-style-type: none"> • GCS: 9-13 	<ul style="list-style-type: none"> • GCS: 3-8

Table 2-2 Civilian Concussion Classification

Mild	Moderate	Severe
<ul style="list-style-type: none"> • No LOC • Confusion < 15 min. 	<ul style="list-style-type: none"> • No LOC • Confusion > 15 min. 	<ul style="list-style-type: none"> • LOC

Table 2-3 Proposed Explosive Blast TBI Classification

Mild	Moderate	Severe
<ul style="list-style-type: none"> • LOC <1 hour • Amnesia <24 hours 	<ul style="list-style-type: none"> • LOC >1 hour but <24 hours • Amnesia >1 day but <7 days 	<ul style="list-style-type: none"> • LOC >24 hours • Amnesia >7 days

GCS = Glasgow Coma Scale; TBI = Traumatic Brain Injury; LOC = Loss of Consciousness

The Injury Severity Score (ISS) was developed as a means to assign a valid numerical description of overall severity of injury in people who have injuries to more than one area of the body. It incorporates body area considerations as well as severity.

This measure is commonly used to be able to compare persons whose injuries may not be anatomically the same but have the same severity (Baker, O’Heill, Haddon & Long, 1974). ISS values and associated severity levels can be seen in Table 2-4. ISS was used to assess severity of injury in this study, even though patients had isolated similar injuries, to allow for easier comparisons with other research studies in the future.

Table 2-4 Injury Severity Score Classification

Minor	Moderate	Moderate/Severe	Severe/Critical
• ISS: 1-9	• ISS: 10-15	• ISS: 16-24	• ISS: ≥ 25

2.2.5 Intracranial Pressure

Intracranial pressure (ICP) is the pressure exerted by the cerebrospinal fluid, blood, and tissue within the rigid bony structure of the skull. If the volume of any one of these components increases, one of the other components needs to decrease in order to maintain ICP (Hickey, 2009). Increasing ICP can result in irreversible injury to the central nervous system by compromising blood flow within the brain and causing death unless treatment is successful. Normal ICP for adults ranges from 0 to 15 mm Hg. Elevations above 20 mm Hg are considered abnormal (Barker, 2008).

Cerebral perfusion pressure (CPP) is the difference between mean arterial pressure and intracranial pressure. CPP is the pressure needed to perfuse the blood up into the brain (Barker, 2008). The goal is to have CPP about 60-70 mm Hg (Bridges, 2009). CPP below 50 mm Hg is often associated with increased levels of extracellular lactate and irreversible ischemia and infarction result when CPP is less than 40 mm Hg (Barker, 2008).

Patient management of head injuries is focused on preventing or treating the increased ICP that accompanies the primary injury. ICP monitoring is indicated in TBI patients who have an abnormal CT scan and a GCS score between 3 and 8. ICP monitoring may also be considered with severe TBI if the patient's CT scan is normal and two of the following apply: age > 40 years, posturing, and systolic blood pressure <90 mm Hg (Barker, 2008).

2.3 Secondary Injuries

Whereas primary brain injury is the immediate response to the initial impact of mechanical force to the head, secondary brain injury is a delayed, physiologic response to the primary injury (Hickey & Prator, 2009). Even though some degree of irreversible damage occurs with the primary injury, TBI is a process in which additional and progressive secondary injury evolves over the minutes, hours, and days following the primary injury (Blank-Reid, McClelland & Santora, 2008; Lovasik, Kerr & Alexander, 2001). Secondary injuries occur as a complication of the primary injury and are a devastating consequence of the body's physiologic mechanisms. Clinical management is focused on preventing or minimizing these secondary injuries. The prospect of a favorable outcome decreases as the number, frequency, or severity of secondary injury increases. Examples of secondary injury are listed in Table 2-5 (Blank-Reid, McClelland & Santora, 2008).

Table 2-5 Secondary Injuries of TBI

Examples of Secondary Brain Injury
<ul style="list-style-type: none">• Cerebral edema• Hypoxia• Hypotension• Hypocapnia• Hyperthermia• Increased Intracranial Pressure (ICP)• Systemic Inflammatory Response Syndrome (SIRS)• Anemia• Electrolyte Disturbances• Vasospasm• Hydrocephalus• Seizures• Infections

TBI rapidly initiates a series of secondary events that together contribute to cell injury and/or repair. These early events can be generalized into three periods, those that arise within minutes after injury, those that evolve over the first 24 hours, and those that may be more delayed appearing between 24 to 72 hours after injury (see Table 2-6). The details about the pathogenic events occurring during these time periods and their interactions are not completely understood. These time periods, therefore, are only an estimation but most extend for days after the TBI occurs. The type and severity of the injury, in part, will determine the variability in onset and frequency, as well as the duration of the pathogenic events (Margulies et al., 2009).

Table 2-6 Initiation of Acute Secondary Events Post-TBI

Within minutes	Minutes to 24 hours post-injury	24 to 72 hours post-injury
<ul style="list-style-type: none"> • Axon stretching, impaired transport, and disconnection; compaction of neurofilaments, • Disruption of the blood-brain barrier • Excessive neuronal activity • Widespread changes in neurotransmitters • Hemorrhage • Seizures • Physiologic disturbances • Increased free radical production • Disruption of calcium homeostasis • Mitochondrial disturbances 	<ul style="list-style-type: none"> • Oxidative damage • Ischemia • Edema • Enzymatic activation • Decreased ATP • Cytoskeleton changes in cell somas and axons • Widespread changes in gene expression • Inflammation 	<ul style="list-style-type: none"> • Non-ischemic metabolic failure

Adapted from Margulies, S., Hicks, R., & Combined Therapies for Traumatic Brain Injury Workshop Leaders, (2009). Combination therapies for traumatic brain injury: prospective considerations. *Journal of Neurotrauma*, 26,925-939.

Many of the secondary insults listed in Table 2-5 can only be diagnosed or assessed using sophisticated equipment in a hospital environment. Therefore, the secondary insults most likely to be seen in this study population of deployed military TBI casualties before returning to the United States include: hypoxia, hypotension, hyperthermia, hypothermia, and hyperglycemia.

For more than 20 years, hypoxia and hypotension have been secondary brain insults that have been associated with adverse outcomes following TBI. A meta-analysis of individual patient data from seven Phase III randomized clinical trials in moderate or severe TBI and three TBI population-based studies reported the occurrence of hypoxia, hypotension or hypothermia prior to or on admission to the hospital in TBI patients as being strongly related to poorer outcomes. Outcome was evaluated at 6-months after TBI as measured by the Glasgow Outcome Scale (McHugh et al., 2007). TBI patients who

present with or develop hyperthermia or hypothermia have worse outcomes than patients with TBI who remain normothermic. Increased body temperature greater than 38° C in patients with TBI is associated with a longer intensive care unit (ICU) and hospital length of stay, higher mortality rate, and worse outcomes (Jiang, Gao, Li, Yu & Zhu, 2002; Stocchetti, Rossi, Zanier, Colombo, Beretta & Citerio, 2002; Diring, Reaven, Funk & Uman, 2004). Secondary hypothermia due to trauma or trauma resuscitation in patients with TBI has been independently associated with longer ICU length of stay, lower Glasgow Coma Score (GCS) at discharge, higher mortality rates, and lower Expanded Glasgow Outcome Scale (GOSE) scores up to 6 months post-injury (Wang, Callaway, Peitzman & Tisherman, 2005; Jeremitsky, Omert, Dunham, Protetch & Rodriguez, 2003). Thus, hyperthermia and secondary hypothermia both are secondary insults of TBI that appear to be associated with poor outcomes. Numerous studies over the last two decades have demonstrated that hyperglycemia is a significant indicator of severity of injury and a significant predictor of outcome in patients with severe brain injury. Early hyperglycemia is associated with a longer hospital length of stay and higher mortality rate in severe brain injury (Jeremitsky, Omert, Dunham, Wilberger & Rodriguez, 2005; Walia & Sutcliffe, 2002). The Glasgow Outcome Scale (GOS) was also used to demonstrate a significant correlation between hyperglycemia and poor neurological outcome (Zygun, et al., 2004; Rovlias & Kotsou, 2000; Lam, Winn, Cullen & Sundling, 1991; Young, Ott, Dempsey, Haack & Tibbs, 1989). These studies all support the conclusion that secondary insults of hypoxia, hypotension, hypothermia, hyperthermia, and hyperglycemia are associated with worse outcomes for TBI patients.

As already discussed, secondary hypotension and hypoxemia are associated with increased mortality and morbidity in closed head injured patients. The effect of these secondary insults on outcome after blast injury, however, is unknown. Compensatory cerebral vascular response offset some of the effects of secondary insults of hypotension and hypoxia in the absence of brain injury. When a blast-induced brain injury occurs, however, these protective responses may be compromised just as they are in other types of TBI leaving the brain vulnerable to the effects of secondary insults of hypotension and hypoxia (DeWitt & Prough, 2009). Until additional animal studies can be done with experimental models that accurately reproduce the effects of blast injury in humans, little is known about secondary insults following bTBI.

The prevalence of a secondary insult is the proportion of patients with the secondary insult at a given point in time. The timing can vary depending on the study question. Following is a discussion of the prevalence and timing of the secondary insults explored in previous studies (see Table 2-7).

Table 2-7 Previous Studies of Secondary Insults of TBI Patients

Study	Sample	N	Secondary Insult	Prevalence	Timing	Outcome	Outcome Timing
Arthurs et al., 2006	Combat trauma injuries	2,848	Hypothermia	18%	Initial reading	Mortality *	Hospital D/C
Chestnut et al., 1993a	Severe TBI	717	Hypoxia		Injury through resuscitation	Mortality ^{1,2}	Hospital D/C
Chestnut et al., 1993b	Severe TBI	493	Hypotension	35%	ICU stay	Mortality *	Hospital D/C
Chi et al., 2006	TBI transported to level I trauma centers by helicopter	150	Hypoxia	25%	Pre-hospital	Mortality ¹	Hospital D/C
			Hypotension	9%		LOS *	
			Both	4%		DRS *	
Diringer et al., 2004	Neurologic ICU patients	4,295	Hyperthermia	33%	ICU stay	Mortality * ICU LOS * Hosp LOS * Hospital disposition *	Hospital D/C
Jeremitsky et al., 2005	ICU Severe TBI	77	Hyperglycemia	NR	ICU days 1-5	Mortality * Hosp LOS *	Hospital D/C
Jeremitsky et al., 2003	Severe cTBI	81	Hypoxia	46%	First 24 hours after injury	Mortality ^{2,3,5}	Hospital D/C
			Hypotension	68%		ICU LOS ¹	
			Hypothermia	26%		Hosp LOS ^{1,2,4,5}	
			Hyperglycemia	42%		Hospital disposition ²	
Jiang et al., 2002	Severe TBI	846	Hypoxia	11%	Within 48 hours post injury	GOS ^{1,4}	1 year
			Hyperthermia	25%			
Lam et al., 1991	Neurosurgical patients	169	Hyperglycemia	33%	Within 24 hours post injury	GOS *	10 days
McHugh et al., 2007	Meta Analysis of Moderate to severe TBI	9,205	Hypoxia	20%	Prior to or on Admission to ED	GOS ^{1,2,3}	6 months
			Hypotension	18%			
			Hypothermia	10%			
Miller et al., 1982		34	Hypoxia	35	Admission to ED	Mortality ^{1,2}	
			Hypotension	15			
Rovlias & Kotsou, 2000	Neurosurgical patients	267	Hyperglycemia	NR	Hospitalization	GOS *	6 months
Shafi et al., 2005	Trauma patients	38,550	Hypothermia	8.5%	Admission to ED	Survival *	Hospital D/C
Shafi & Gentilello, 2005	Trauma vs. cTBI patients	79,478	Hypotension	3%	Admission to ED	Mortality [†]	Hospital D/C
Stocchetti et al., 2002	ICU TBI	110	Hyperthermia	73%	First week post trauma	GOS ICU LOS *	6 months
Stocchetti et al., 1996	Head trauma patients rescued by helicopter	49	Hypoxia	57%	On scene	GOS ^{1,2}	ICU D/C
			Hypotension	20%			6 months
Walia & Sutcliffe, 2002	Severe TBI	338	Hypotension	NR	First 24 hours after injury	Mortality ^{2,5}	Hospital D/C
			Hyperglycemia	NR			
Wang et al., 2005	Trauma patients	38,520	Hypothermia	5%	Admission to ED	Mortality *	Hospital D/C
Young et al., 1989	TBI patients	59	Hyperglycemia	48%	First 7 days after injury	GOS *	18 days, 3 mos, 1 year

* = Patients with secondary insult had statistically significant outcome. † = Hypotension does not increase mortality in TBI patients more than it does in non-TBI patients.

1-5 = Outcome was statistically significant for secondary insult indicated: 1- hypoxia, 2-hypotension, 3-hypothermia, 4-hyperthermia, 5-hyperglycemia. cTBI-closed head TBI; D/C-discharge; DRS-Disability Rating Scale; GOS-Glasgow Outcome Scale; ICU-intensive care unit; LOS-length of stay; NR-not reported; TBI-traumatic brain injury.

2.3.1 Hypoxia

The prevalence of hypoxia as a secondary insult in the TBI studies reviewed ranged from 11% found by Jiang et al. (2002) in the first 48 hours after injury to 57% reported by Stocchetti, Furland & Volta (1996) on the scene of head trauma patients rescued by helicopter. Hypoxemia is thought to be more frequently detected and promptly corrected (Stocchetti, Furland & Volta, 1996). This may account for the high prevalence of hypoxia when assessed on the scene. It also leads one to question if hypoxia occurred earlier, was detected, and corrected by first responders before arriving at the hospital where many of the other studies began their assessment. If this is the case, the prevalence of hypoxia as a secondary insult during the acute phase of TBI could be vastly underreported.

2.3.2 Hypotension

Hypotension occurred in 9% to 68% of the TBI study samples reviewed. Chi et al. (2006) reported a 9% prevalence rate of hypotension in pre-hospital TBI patients being transported by helicopter. The average transport time in this study was 75 minutes. Since this was a pre-hospital study, the short duration of an average of 75 minutes, could account for the low prevalence of hypotension. This same rationale could be used to explain Jeremitsky et al.'s (2003) 68% hypotension prevalence since their study included the first 24 hours after injury. Where most of the studies reviewed utilized a period of time, whether it be pre-hospital, ICU stay, or a defined timeframe, to assess hypotension, Shafi & Gentilello (2005) used the first systolic blood pressure on arrival in the emergency department. By using just this one time point, the prevalence of hypotension

they found in their study was 4.4% for trauma patients with a cTBI compared to 2.6% for trauma patients with no TBI.

2.3.3 Hypothermia

Hypothermia can be accidental or intentional. Accidental hypothermia is associated with stress and shivering. Its duration is likely variable, uncontrolled, and transient. Intentional hypothermia, on the other hand, has been thought to be beneficial for selected patients with isolated disease processes such as cardiopulmonary resuscitation and selected patients with TBI. Induced hypothermia controls the stress and shivering found in accidental hypothermia and involves a prolonged and sustained time period (Wang, Callaway, Peitzman & Tisherman, 2005). Other factors to be considered with the development of hypothermia are seasonal and environmental considerations. In the meta-analysis conducted by McHugh et al. (2007), a strong seasonal effect for hypothermia was found with a substantial increase in prevalence from October through February. Additionally, Arthurs et al. (2006) in their report of the impact of hypothermia on trauma care at a deployed combat support hospital cautions about the potential risk of exacerbating hypothermia when transporting patients by the air evacuation system.

The prevalence of hypothermia ranged from 5% to 10% for studies assessing hypothermia on admission. Arthurs et al. (2006) reported an 18% prevalence of hypothermia on the initial reading in combat casualties at a deployed combat support hospital and Jeremitsky et al. (2003) reported a hypothermic prevalence of 26% in the first 24 hours after injury.

2.3.4 Hyperthermia

The prevalence of hyperthermia in the studies reviewed ranged from 25% in the study by Jiang et al. (2002) where they monitored for hyperthermia for 48 hours after injury to 73% in the study by Stocchetti et al. (2002) which included a one week post-trauma evaluation period. Hyperthermia is thought to worsen injury even if it occurs 24 hours after the original insult (Diringer, Reaven, Funk & Uman, 2004) therefore, the longer study periods are appropriate for evaluating the effects of acute hyperthermia. Some of the variability between findings may be associated with inconsistent temperature cut points used by the researchers for the definition of hyperthermia.

2.3.5 Hyperglycemia

Several of the studies reviewed did not report the prevalence of hyperglycemia. Of the studies that did, Jeremitsky et al. (2003) reported a hyperglycemia rate of 42% within the first 24 hours after injury and Lam, Winn, Cullen & Sundling (1991) reported a prevalence of 33% in the first 24 hours after injury. A 7 day post-injury assessment period was used by Young, Ott, Dempsey, Haack & Tibbs (1989) for the study they used which resulted in a hyperglycemia prevalence of 48%. The studies that did not report prevalence had study periods ranging from first 24 hours after injury to hospital length of stay.

2.4 Outcomes

Almost 30 years ago, Humphrey and Oddy (1980) reported that the outcome for the survivors of severe head injury had been difficult to compare and interpret due to the variety of outcome measures used, the inconsistencies found, and the diversity of studies. Different criteria had been used for the severity of injury, age distributions, and follow up

periods. Measures of assessment also varied with the focus fluctuating between physical, social, cognitive and personality factors. Unfortunately, researchers of severe TBI are still struggling with some of these same issues.

Many of the human studies of severe TBI use large trauma databases. These retrospective secondary data analysis studies are dependent on the information provided in the database. Long term outcomes are often not available contributing to the researchers' choice of utilizing available data for the outcome variable, often hospital mortality, length of stay, and hospital disposition. Prospective designs, even though often much smaller in sample size, allow for a much larger choice of outcome variables. A variety of outcome scales are available but the one most often seen, when used, in the study of secondary insults of severe TBI patients is the Glasgow Outcome Scale (GOS). The lack of an objective scale to assess outcome after brain damage led to the development of the GOS (Jennett & Bond, 1975). This five point scale includes death, persistent vegetative state, severe disability (conscious but disabled), moderate disability (disabled but independent), and good recovery.

The most commonly used outcome variables in the studies of secondary insults of TBI reviewed include mortality, length of stay, hospital disposition, and GOS (see Table 2-7).

2.4.1 Hypoxia

Three studies reviewed found those patients with the secondary insult of hypoxia had a significantly higher rate of mortality (Chestnut et al., 1993a; Chi et al., 2006 & Miller et al., 1982). Jeremitsky et al. (2003), however, found that even though those patients with hypoxia had a significantly longer ICU and hospital length of stay, mortality

was not significantly increased. All three studies with hypoxia as a secondary insult and GOS as an outcome measure demonstrated a statistically significant worse outcome on the GOS scale for those patients that had experienced a hypoxic episode (Jiang et al., 2002; McHugh et al., 2007 & Stocchetti et al., 2002). Even though McHugh's meta-analysis reported a statistically significant worse outcome for those with hypoxia, patients with both a hypoxic and hypotensive event had even worse outcomes than either insult alone (2007).

2.4.2 Hypotension

Both the meta-analysis by McHugh et al. (2007) and the prospective study by Stocchetti et al. (1996) demonstrated a significantly worse GOS outcome for those patients with a hypotensive episode. Increased mortality was also related to TBI patients who were hypotensive in six of the studies reviewed. Chi et al. (2006), however, did not find a significant increase in mortality even though length of stay was significantly longer for TBI patients with a hypotensive episode. An important comparison in regard to hypotension was brought up in the study by Shafi and Gentilello (2005). In their study of 79,478 trauma patients, hypotension was a significant predictor of mortality. When TBI patients were compared to non-TBI patients, however, the difference was not statistically significant leading them to contend that hypotension does not increase mortality in brain-injured patients more than it does in non-brain-injured patients.

2.4.3 Hypothermia

Hypothermia was found to have a significant association with worse GOS at 6 months in the meta-analysis conducted by McHugh et al. (2007). TBI patients with hypothermia were also found to have significantly worse mortality than normothermic

patients (Arthurs et al., 2006; Jeremitsky et al., 2003; Shafi et al., 2005 & Wang et al., 2005). Shafi, Elliott & Gentilello (2005) pose to test the assumption that induced hypothermia offers potential protective effects in trauma patients in their study of 38,550 trauma patients. Even when controlled for injury severity and various potential confounders, they found that hypothermia remained a strong independent predictor of mortality leading them to contend that there is no apparent protective effect of hypothermia in trauma patients (Shafi, Elliott & Gentilello, 2005).

2.4.4 Hyperthermia

The study by Stocchetti et al. (2002) found 73% of their sample of 110 ICU TBI patients developed hyperthermia within the first week post trauma. These patients had a significantly longer ICU length of stay but. Their 6-month GOS outcome was not significantly different, however, than normothermic ICU TBI patients. Jiang et al. (2002), however, found a significantly worse GOS outcome at one year for the 846 severe TBI patients studied. In addition, a large retrospective review of 4,295 neurologic ICU patients demonstrated a significantly worse outcome in mortality, ICU LOS, hospital LOS, and hospital disposition for hyperthermia patients (Diringer et al., 2004).

2.4.5 Hyperglycemia

TBI patients with hyperglycemia have demonstrated significantly worse outcomes in mortality, hospital LOS, and GOS. Even though assessment using the GOS ranged from 10 days to 1 year, all revealed a significantly worse outcome for hyperglycemic patients (Lam et al., 1991; Rovlias & Kotsou, 2000 & Young et al., 1989). Mortality was associated with TBI patients with hyperglycemia whether they developed the hyperglycemia within the first 24 hours after injury or later in their ICU course

(Jeremitsky et al., 2005; Jeremitsky et al., 2003; Walia & Sutcliffe, 2002). The studies by Jeremitsky et al. (2005 & 2003) also revealed a significant association between severe TBI patients with hyperglycemia and a longer hospital length of stay.

2.5 Impact of Flight

Severely injured military TBI casualties are transported from the war zone by Critical Care Air Transport Teams (CCATT). The U.S. Air Force developed the CCATT concept in 1994 in response to a need for long-range air and ground support of critically ill and injured patients. The CCATT teams have dramatically reduced the time from injury to resuscitation and surgery contributing to the lowest died-of-wounds rate in the history of modern warfare (Grison & Farmer, 2005; Sario, 2006). The CCATT team transports critically ill patients on a variety of military cargo aircraft. The team is capable of transforming any aircraft into a mobile critical care unit (Collins, 2008). This requires the team to bring with them all necessary and anticipated ventilators, monitors, IV infusion pumps, suction equipment, medications and other equipment necessary to sustain and support the critically ill patients (Johannigman, 2007). These transports, lasting as long as eight to fourteen hours, take place in an environment of noise, vibration, cramped space, and low light (Richardson, 2007). In addition to these challenges, TBI patients are exposed to the stresses of flight encountered on cargo aircraft to include decreased barometric pressure, decreased partial pressure of oxygen, decreased humidity, temperature fluctuations, noise, vibration, fatigue, and sometimes motion sickness (Richardson, 2007; Clark, Bair, Buckenmaier, Gironda & Walker, 2007). This study not only explored secondary insults of TBI CCATT patients, but also CCATT

transportation times for a 5 year period from 2001 to 2006 allowing a comparison of transportation times over the course of the database.

2.5.1 Stresses of Flight

Eight classic stresses of flight exist: decreased partial pressure of oxygen, barometric pressure changes, vibration, thermal changes, decreased humidity, gravitational forces, noise, and fatigue (Holleran, 2003). The combination of these physiologic stresses encountered at altitude act in a cumulative manner and although fatigue is identified as a separate stress of flight, it also is the end product of the other seven (Hickman & Mehrer, 2001).

As altitude increases, the pressure on all gases, including oxygen, is decreased. This decrease in the partial pressure of oxygen leads to hypoxia if compensatory measures are not initiated. Lower levels of oxygen in the TBI patient can cause brain cell and tissue ischemia and ultimately brain cell death. Resulting cerebral edema and increased intracranial pressure leads to hypoventilation and further hypoxemia. Even just one hypoxic episode in the presence of TBI can lead to a catastrophic secondary brain injury (Air Force Instruction, 2007).

Barometric pressure changes cause gas to expand when altitude increases and to contract on descent. As a result, trapped gases within body cavities expand in direct proportion to the decrease in pressure. For example, 1 liter of gas at sea level becomes 1 ½ liters at 9,000 feet (Air Force Instruction, 2007). Depending on the aircraft and route, the ambient altitude is often between 30,000 and 38,000 feet. The cabin, however, is pressurized to levels between 5,000 to 10,000 feet (Beninati, Meyer & Carter, 2008; Dufour, 2003; Johannigman, 2008; Pierce & Evers, 2003). The expansion of gas with

increasing altitude was confirmed by a simulation model which indicated that under normal flying conditions with decreased cabin pressure at a cabin altitude of 8,000 feet, air volume increased by approximately 30 percent. An intracranial air volume of 30 milliliters would increase the intracranial pressure of 20 mm Hg at sea level to 31.8 mm Hg at a cabin altitude of 8,000 feet (Andersson et al., 2003). In an effort to protect the patient from the effects of gas expansion, conditions that introduce air into the body which are becoming more common in the settings of injuries caused by improvised explosive devices in OIF/OEF, medical flight crews need to seek out any potential sights of free gas prior to flight (Johannigman, 2008).

Vibration is often encountered during flight. Mechanical energy is transferred when the human body is in direct contact with a source of vibration. This energy is degraded into heat within tissues with dampening properties. An increase in muscle activity is the response to whole body vibration which is reflected in an increase in metabolic rate and peripheral vasoconstriction. The increase in basal temperatures from the increased metabolic rate along with the vasoconstriction can contribute to heat exhaustion and dehydration. The elevated temperature can also contribute to motion sickness and vomiting resulting in increased intracranial pressure in the TBI patient (Air Force Instruction, 2007; Hickman & Mehrer, 2001). Vibration is further amplified when aeromedical evacuations are carried out under tactical settings. During a tactical takeoff, the aircraft commander will attempt to gain altitude as rapidly as the airframe will permit to gain safe altitude. This situation is reversed during landing as the aircraft commander attempts to descend from a safe altitude to the runway as rapidly as possible. During

these times, the ascent/descent is rapid, aggressive, and often turbulent (Johannigman, 2008).

A decrease in ambient temperature occurs as altitude increases. The aircraft cabin temperature can fluctuate considerably depending on the temperature outside the aircraft. Inside aircraft temperature variations can range from 59°F or lower to 77°F during winter flying and in the summer from 68°F to greater than 95°F (Air Force Instruction, 2007). It can be very difficult to control and maintain a constant temperature throughout the aircraft cabin. Cabin temperature may be extremely warm in one area and cold in another. A study assessing thermal stress and human responses onboard aeromedical evacuation aircraft demonstrated a thermal gradient in which the warmest location was the front of the cargo hold near the ceiling and the coldest location was the rear of the cargo hold near the floor (Schmelz, Bridges, Duong & Ley, 2003). The placement of patients in the aircraft cabin will depend on the number and acuity of patients being transported, other cargo or passengers manifested, and the flight plan for the mission.

Air loses its ability to hold moisture when it is cooled. Air at altitude is cold and possesses very little moisture; the higher the altitude, the colder and drier the air. The fresh air is drawn into the aircraft cabin from a very dry atmosphere. After 2 hours of flying time on a typical flight, there is less than 5 percent relative humidity. After 4 hours, relative humidity is less than 1 percent. Decreased humidity in the TBI patient can dry the corneas of patients with decreased corneal/blink reflex and increase dehydration and headaches (Air Force Instruction, 2007; Schmelz, Bridges, Duong & Ley, 2003).

Acceleration and deceleration fore and aft along the longitudinal axis is the most important gravitational force to be aware of in aeromeical transport. When the aircraft

accelerates or decelerate, the already swollen or bruised brain of a TBI patient could experience further damage. Patients in litters are normally placed with their feet toward the front of the aircraft. When an aircraft takes off, blood rushes from the lower extremities to the head in a patient laying flat increasing intracranial pressure (Air Force Instruction, 2007; Dufour, 2003).

Unprotected exposure to noise can produce undesirable effects to include interference with communications, auditory fatigue, and hearing loss (Air Force Instruction, 2007). The average ambient noise levels inside the cabin of a C-130 aircraft approach 85 dB (Johannigman, 2008). In this environment, auscultation of heart and lung sound is almost impossible and the use of a manual blood pressure cuff and stethoscope are difficult to use effectively (Schmelz, Bridges, Duong & Ley, 2003). Adequate ear protection is warranted even for comatose patients. Hearing should be protected since loud noises can be aggravating to the already uncomfortable patient and hearing is the last sense to go and the first to come back (Dufour, 2003).

All of the stresses of flight produce fatigue to some degree. Fatigue is the end product of all the physiological and psychological stresses associated with exposure to altitude. Therefore, in transport, fatigue is always a potential threat to safety (Holleran, 2003).

2.5.2 Characteristics of Aircraft

Even though CCATT teams are flexible enough and have the problem solving skills to perform on whatever opportune aircraft is available, most strategic missions in the recent past have been conducted on C-141s and C-17s. These longer intertheater

missions require aircraft that are capable of flying long distances (Beninati, Meyer & Carter, 2008; Pierce & Evers, 2003).

The C-141 is no longer being used by active duty Air Force units, but it is still being flown by reserve and guard units and has played a key role in medical evacuation in OIF/OEF (B.E. Holmgren, personal communication, 14 October 2009). The C-141 has the capacity for up to 103 litter patients. The number of patients and the patient configuration will determine whether access to the patient is limited to 180 degrees or a full 360 degree access is possible. A therapeutic oxygen manifold system is available for litter patients. The electrical system however provides 400 Hz AC power through specially configured outlets which limits the direct usefulness for medical devices. Medical teams must rely on battery power or power provided through an electrical converter. Lighting and environmental control systems are minimal requiring additional measures for patient warming and visualization of patient care. The noise within the aircraft is loud making communication difficult (Air Force Instruction, 2000; Air Force Medical Service, 2001).

The C-17 Globemaster III is an excellent aircraft for both tactical and strategic evacuation. Its unrefueled range of 2,400 nautical miles and unlimited range with aerial refueling makes it useful for transoceanic missions. It is well lit and the system of litter stanchions provides 360 degree access to critical patients. The aircraft has built-in systems that provide medical oxygen at 50 pounds per square inch and 60 Hz AC electric power through standard U.S. outlets. The C-17 can be quickly configured from use as a cargo aircraft to accommodate 36 litter patients (USAF Factsheet C-17, 2008; Beninati,

Meyer & Carter, 2008). The noise level is reduced in the C-17 making communication relatively easy (Air Force Medical Service, 2001).

2.5.3 Duration of Flight

The first seven days post TBI for most deployed critically injured casualties are spent in the process of trying to return to the United States. During this transport process, casualties travel thousands of miles, come in contact with healthcare providers from all different military services, and pass through multiple hospital systems (Clark, Bair, Buckenmaier, Girona & Walker, 2007). On average, patients remain “in theater” 28 hours from the point of injury until being evacuated to Germany by CCATT (Johannigman, 2008). The average flight time from the area of responsibility (AOR) to Landstuhl Regional Medical Center (LRMC) in Germany is over 6 hours with median preflight and post flight ground times of 30 minutes (Bridges & Evers, 2009). Once at LRMC, the average ICU stay is 72 hours (Fang et al., 2009). Subsequent CCATT flights from LRMC to the contiguous United States (CONUS) can take as long as 8-14 hours (Richardson, 2007). The median time from the point of wounding to arriving at a tertiary hospital in CONUS was reported by Fox, et al. (2005) to be 8.5 days. The differences in flight/transport times between studies may be attributed to periods of measurement. For example, CCATTs assume care in the sending hospital and transfer care at the receiving hospital which includes ground transport. The duration of CCATT care, therefore, will be longer than just the flight duration. Some of these studies also include both routine medical air evacuation flights as well as CCATT flights. Also, the duration of some of these studies cover a shorter period of time. This study which covers a five year period

from October 2001 to May 2006 will provide a picture as to whether transport times have changed over this five year period for CCATT patients with TBI.

2.6 Levels of Care for Combat Injuries

Military medicine is traditionally sorted into five levels of care delivery for combat injuries (Baker, Buckenmaier, Narine, Compeggie, Brand, & Mongan, 2007). Level 1 includes self-aid, buddy care, and advanced trauma life support provided by a mobile emergency room setup. Level 2 is the first level at which surgical intervention is performed and usually consists of life-and-limb salvage or “damage control” surgery and has limited patient holding capacity. Level 1 and Level 2 units, at times, may be co-located. Medical evacuation between Level 2 and Level 3 care is usually by helicopter with en route care nurses for the severely injured. Level 3 hospitals are designed to be mobile but have six or more operating rooms with surgical specialties available. In prior conflicts, wounded soldiers spent many days to weeks recovering from wounds in field hospitals before they were considered stable enough for transport back to major hospitals. Now, most patients whose injuries do not allow them to return to duty in 7 days are leaving Iraq from Level 3 centers within 24 to 48 hours (Baker, Buckenmaier, Narine, Compeggie, Brand, & Mongan, 2007; Collins, 2008; Smith, 2008). CCATT teams transport critical patients from Level 3 centers to Level 4 hospitals. These are major hospitals out of the theater of operation but still outside of the continental United States, such as Landstuhl, Germany. CCATT teams are also used to transport critical patients from the Level 4 hospitals back to Level 5 hospitals in the United States. These Level 5 hospitals are located across the United States where further evaluation and treatment is given. In some cases, patients are reaching Level 5 hospitals as soon as 48 hours after

injury, although the average is 6 to 7 days (Fox, et al., 2005; Fang, et al., 2008; Collins, 2008).

2.7 Summary

Explosive blasts are inflicting injuries resulting in varying clinical profiles often different than those of penetrating or closed head injuries. These differences along with the complicated picture of the OIF/OEF casualty and the prolonged austere transport environment create a picture of CCATT TBI patients much different from civilian TBI patients that have been studied in the past. There is no doubt that secondary insults of TBI contribute to worse outcomes. What is not known is what kind of secondary insults are occurring in CCATT TBI patients and at what point in the transport process they occur. It is hoped by identifying these trends, preventive measures can be implemented to decrease the occurrence of secondary insults thus contributing to improved outcomes.

Chapter 3: Methods

3.1 Overview

This chapter describes the methods used to answer the research aims. Study design, data source, variables, sample, human subjects' protection, research file development, data assumptions, and data analysis procedures are described.

3.2 Design

A retrospective cohort design was used. Casualties with isolated TBI (single body system injured) were identified utilizing the Wartime Critical Care Air Transport database (Bridges & Evers, 2009). Data in this database allowed identification of the frequency and timing of the secondary insult factors of hypoxia, hypotension, hypothermia, hyperthermia, and hyperglycemia. This study follows patients through five time periods, or legs, which include point of injury to Area of Responsibility Medical Treatment Facility (AOR MTF), care while at the AOR MTF, Critical Care Air Transport from the AOR to Landstuhl Regional Medical Center in Germany (LRMC), care while at LRMC, and CCATT from LRMC to the contiguous United States (CONUS) (See Figure 3-1).

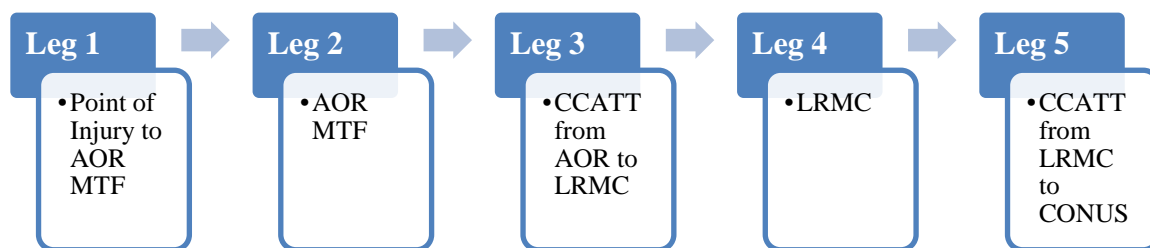


Figure 3-1 Study Legs

AOR – Military Area of Responsibility; MTF – Medical Treatment Facility; CCATT – Critical Care Air Transport Team; LRMC – Landstuhl Regional Medical Center in Germany; CONUS – Contiguous United States

3.3 Data Source

3.3.1 Wartime Critical Care Air Transport Database

The Wartime Critical Care Air Transport Database (WCCATD) integrates data from multiple sources to include: 1) U.S. Transportation Command and Control Evacuation System (TRAC²ES), 2) CCATT Mission Reports, 3) Joint Theater Trauma Registry, and 4) retrospective medical record review. Patients in this database are those who were transported by USAF CCATT in support of OEF/OIF from October 2001 through May 2006 (Bridges & Evers, 2009).

TRAC²ES data are collected at the individual level for the purpose of tracking aeromedical evacuations. Logistic information, transportation requirements, and clinical decision-support elements are combined to provide complete visibility of all patient movement to the medical transportation needs of the Department of Defense. TRAC²ES is used when transporting patients to fixed inpatient facilities and beyond. Other medical transportation may have been used before the patient was entered into TRAC²ES and patients not requiring transport to a fixed inpatient facility are not included. TRAC²ES was not designed as a research database so, often only the most vital information required for the purposes of patient transport is entered. Studies by both Harman (2005) and Bridges & Evers (2009) found a substantial number of fields with missing data in the TRAC²ES database. Since the TRAC²ES database is part of the WCCATD, these missing data contribute to the missing data issue in this study.

CCATT Mission Reports are completed by CCATT members for each patient transported. Whereas TRAC²ES and the CCATT Mission Reports provide patient information from the point the patient enters the fixed wing transportation system, the

Joint Theater Trauma Registry provides information from the time of injury or event to presentation at a medical facility and to evacuation out of theater. The retrospective review of medical records provided additional information on the confirmed diagnosis for each patient, in-flight care to include such things as fluid resuscitation, equipment, and medical requirements, the patient's enroute physiological status to include vital signs, oxygenation/ventilation status, pain, and fluid status, and enroute and acute outcomes (Bridges & Evers, 2009).

The combination of data sources used in the creation of the Wartime Critical Care Air Transport Database provides coverage of the entire period from the point of injury to the patient's arrival in a tertiary hospital in the United States to include acute outcomes. The primary problem is one of missing data. All of the ideal data elements listed in Table 7 are included in the Wartime Critical Care Air Transport Database. If the information was not available in the primary source, it is reflected as missing data in the Wartime Critical Care Air Transport Database.

3.3.2 Reliability and Validity of Database

The reliability of secondary data reflect the reproducibility of the data where data collected by different methods, by different people, and at different sites provide the same results (Johantgen, 2005). One way to check the reliability of the data is to examine other variables within the same data set. This is possible within the Wartime Critical Care Air Transport Database. Many of the demographic variables are duplicated since multiple sources were utilized in compiling the database. By comparing these duplicated variables, it is possible to be assured these data elements are reliable. Another way of assessing reliability is to compare results found with analyses of existing data with other

sources of the same information. Table 3-1 shows a comparison of selected results of an analysis of the Wartime Critical Care Air Transport Database (Bridges & Evers, 2009) with the results shown by Mason, Eadie & Holder (2008) in their prospective observational study of CCATT patients transported from Iraq to Germany from September 2005 to August 2006. The similarities of this comparison further support the reliability of the Wartime Critical Care Air Transport Database.

Table 3-1 Comparison of Study Results of CCATT Patients

Characteristic	Mason, Eadie & Holder	Bridges & Evers
Study Design	20% of total CCATT patients transported from Balad, Iraq to Landstuhl, Germany from Sept '05 to Aug '06 (n=133).	Subset of Wartime CCATT Database: CCATT patients transported from AOR to Landstuhl, Germany from Oct '01 to May '06 (n=1,995).
Mean Flight Time	5.0 hours direct; 9.1 hours with 1 stop	6.3 hours
Trauma Patients	65%	75%
Medical Patients	35%	25%
Mean Age	32 years	30 years
Mean Age of Trauma Patients	27 years	27 years
Mean Age of Medical Patients	41 years	40 years
Male	92%	94%
Military Members	83% (US)	88% (All Nations)
Cardiac Conditions	68%	55%

CCATT – Critical Care Air Transport Team; AOR – Military Area of Responsibility

The validity in secondary data indicates how closely the data elements from the database fit the needs of the researcher in conducting the study and answering the research question (Johantgen 2005). Fortunately, the ideal data elements desired for this study already discussed above are primarily demographic and physiologic in nature. This makes it easier to assure that the data elements in the database are the ones desired for conducting the research. Another issue with validity is the amount of missing data. The

desired data elements are included in the database but whether data has been obtained for each element from each patient is quite another issue. Many factors contribute to the high amount of missing data. Some of these factors include the critical nature of the circumstances surrounding the data collection points leading to physiological measures not being recorded and not being able to access the primary sources of the data such as missing flow sheets or lost medical records. As in many types of analyses, missing data can cause problems. Unless missing data are missing completely at random, the estimated coefficients may be biased (Norusis, 2007). Moreover, outcome variables such as hospital disposition, functional status indicators, and/or Glasgow Outcome Scale measures would have allowed assessment of study variables in relation to outcome. As it is, over half of the study participants do not have hospital disposition documented.

3.4 Variables

The data elements used to capture the secondary insults of TBI are included in Table 3-2. These data elements are aligned with the study leg from which they were collected.

Table 3-2 Study Legs and Variables

Leg 1: Point of Injury to	Leg 2: AOR MTF	Leg 3: CCATT AOR to	Leg 4: LRMC, Germany	Leg 5: CCATT LRMC to	CONUS
Gender	Lowest SBP	Date/Time CCATT Assumed Care	Lowest SBP	Date/Time CCATT Assumed Care	Date/Time CCATT Relinquished Care
Age	Lowest SpO ₂	Length of Flight	Lowest SpO ₂	Length of Flight	
Service	Highest Temperature	Lowest SBP	Highest Temperature	Lowest SBP	
Date/Time of Injury	Lowest Temperature	Lowest SpO ₂	Lowest Temperature	Lowest SpO ₂	
Etiology of TBI: non-blast vs. blast	Highest Glucose	Highest Temperature	Highest Glucose	Highest Temperature	
Extent of Injury: Isolated TBI vs. TBI & polytrauma	Highest ICP	Lowest Temperature	Highest ICP	Lowest Temperature	
Injury Severity Score	Lowest CPP	Highest Glucose	Lowest CPP	Highest Glucose	
Initial GCS	Date/Time Arrived	Highest ICP	Date/Time Arrived	Highest ICP	
Initial GCS Motor		Lowest CPP		Lowest CPP	
Lowest SBP					
Lowest SpO ₂					
Highest Temperature					
Lowest Temperature					
Highest Glucose					
Highest ICP					
Lowest CPP					

AOR - Area of responsibility; MTF - medical treatment facility; CCATT – Critical care air transport team; LRMC – Landstuhl Regional Medical Center; CONUS – Contiguous United States; TBI – traumatic brain injury; SBP – systolic blood pressure; SpO₂- Oxygen saturation; GCS – Glasgow Coma Scale; ICP – Intracranial pressure; CPP – Cerebral perfusion pressure.

For operational definitions of the variables used in this study, refer to Table 3-3.

The variables used from the WCCATD and the coding of variables for this study can be found in the appendix (See Table A-1).

Table 3-3 Study Variables and Definitions

Concept	Variable	Operational Definition
Secondary Insults	Hypotension	SBP < 90 mm Hg
	Hypoxemia	SpO ₂ < 90%
	Hyperglycemia	Blood glucose > 200 mg/dL
	Hyperthermia	Temperature > 38.5°C
	Hypothermia	Temperature < 35.0°C
Injury Characteristics	Etiology of TBI	Blast vs. Non-blast injury
	Injury Severity Score	Minor: 1-9
		Moderate: 10-15
		Moderate/Severe: 16-24
		Severe/Critical: ≥ 25
Glasgow Coma Scale	Mild: 14-15	
	Moderate: 9-13	
	Severe: 3-8	
Intracranial Pressure	ICP > 20 mm Hg	
Cerebral Perfusion Pressure	CPP < 60 mm Hg	

3.5 Sample

A subset of isolated head injury patients were examined in this study. Subjects include any casualty with a traumatic brain or head injury who does not have any other body area injured except for minor abrasions, lacerations, or digit amputations. An isolated TBI patient population was utilized in an attempt to explore secondary insults resulting from TBI versus various potential causes in polytrauma patients. All patients over the age of 18 years and all years of the database (Oct '01 – May '06) were included. The WCCATD is intended to capture the entire population of isolated TBI CCATT casualties. Three patients with no physiologic study variables recorded were excluded resulting in a sample size of 64 isolated TBI patients used for analysis.

3.6 Human Subjects Protection

Permission to conduct this study was obtained through an expedited Institutional Review Board (IRB) at the University of Maryland (See Appendix B). This study used

de-identified secondary data. Subject informed consent was not required. A Data Use Agreement (DUA) with the Primary Investigator of the Wartime Critical Care Air Transport Database study was signed in January 2010 (See Appendix C). This DUA outlines responsibilities, data management, and disclosure protection specifics.

3.7 Research File Development

The data were received from the Primary Investigator of the Wartime Critical Care Air Transport Database in an SPSS dataset. Data manipulation and analysis were performed using SPSS 15.0. The Wartime Critical Care Air Transport Database contained multiple rows of data for each patient. This data were transcribed into a short and wide format which contained each patient's data in one row with variables of interest aligned by leg. Table A-1 Variable Values and Origins in the appendix specifies the variables, labels, values, where in the Wartime Critical Care Air Transport Database the new variables were obtained, and any additional corresponding notes. A random sample of 10 percent of the cases was reviewed for accuracy in transcription with 100 percent congruence.

Additional variables were created to meet the study aims. Table A-2 New Variable Values and Origins, in the appendix, details the variables, labels, values, and origins of the new variables as well as any additional corresponding notes.

3.8 Data Assumptions

3.8.1 Normality

Normality of continuous variables was assessed using histograms, statistics and assessment of distributions. Age, days from injury to arrival at LRMC, and days from injury to arrival in CONUS were positively skewed and Injury Severity Scores revealed a

normal distribution (See Table A-3 in the Appendix). Since the assumptions regarding the distributions of predictors are not required for logistic regression (Tabachnick & Fidell, 2007) or for non-parametric tests, the original variables were retained for analysis.

3.8.2 Outliers

Outliers are values very different from the rest of the data (Field, 2005) and were assessed by box plots and histograms. Outliers can bias results when parametric tests are utilized. A case-by-case review of the outliers was conducted with values reported plausible. Since the study sample represents the entire population of isolated TBI CCATT patients, the decision was made to retain the outliers and utilize non-parametric tests.

3.8.3 Missing Data

The data from the WCCATD are balanced and incomplete. Balanced refers to the design of the longitudinal study where participants are measured at the same time points (Fitzmaurice, Laird & Ware, 2004). Completeness refers to the data themselves. Complete data occur when there are no missing data. Incomplete data indicate missing data; observations were planned but not realized (Fitzmaurice, Laird & Ware, 2004). The Wartime CCAT Database does contain missing data so is therefore characterized as incomplete.

Table 3-4 details the missing data in the variables of interest. Very few of the cases had flight time for either of the transports from the AOR to LRMC or from LRMC to CONUS. Therefore, time was assessed by taking the deference between the date of injury and the date of CCATT transport. ICP and CPP were not included in the missing variables analysis since both ICP and CPP are monitoring modalities used only on select

patients therefore it is not possible to determine whether any of the variables are missing or just not assessed. ICP and CPP were used only for subgroup analysis.

Table 3-4 Missing Variables

Variable	N missing	Missing %
Gender	0	0
Age	0	0
Service	0	0
Date of Injury	0	0
Injury Etiology	0	0
Injury Severity Score	5	8
Initial GCS	3	5
Initial GCS Motor	7	12
Leg 1		
Lowest SBP	4	6
Lowest SpO ₂	53	83
Highest Temp	8	13
Lowest Temp	8	13
Highest Glucose	57	89
Date Arrived at Leg 2	19	30
Leg 2		
Lowest SBP	30	47
Lowest SpO ₂	29	45
Highest Temp	33	52
Lowest Temp	33	53
Highest Glucose	36	56
Date Leg 3 Begins	27	42
Leg 3 Aircraft	3	5
Leg 3 Flight Time	58	91
Leg 3		
Lowest SBP	33	52
Lowest SpO ₂	34	53
Highest Temp	40	63
Lowest Temp	40	63
Highest Glucose	58	91
Date Arrived at Leg 4	8	13
Leg 4		
Lowest SBP	20	31
Lowest SpO ₂	24	38
Highest Temp	20	31
Lowest Temp	21	33
Highest Glucose	23	36
Date Leg 5 Begins	15	25
Leg 5 Aircraft	23	39
Leg 5 Flight Time	57	97
Leg 5		
Lowest SBP	35	59
Lowest SpO ₂	37	63
Highest Temp	42	71
Lowest Temp	42	71
Highest Glucose	55	93
Date Arrived at CONUS	16	27
Disposition	31	53

Note: Leg 5 n=61

Joint Theater Trauma System (JTTS) clinical practice guidelines for severe head trauma patients include aggressive temperature management, aggressive avoidance of hypoxemia, avoidance of hypotension, and a low threshold for initiation of an insulin drip. In an effort to meet these guidelines, blood pressure, pulse oximetry, and temperature are monitored frequently if not continuously and laboratory studies to include blood glucose levels are recommended at least every 8 hours (Bridges, 2009). Glucose levels were consistently the physiologic measure least documented. This is not surprising since blood glucose is the physiologic parameter of the five study variables assessed least often.

There is no doubt that medical resources are limited in the far forward areas of the battlefields. Therefore, the limited oxygen saturation and glucose data for Leg 1 could be a function of limited monitoring equipment. Given the extreme amount of missing data for these two variables in contrast to blood pressure and temperature, one must ask if this is a systems or documentation issue. The data used for the Leg 1 oxygen saturation and blood glucose levels were obtained from narrative fields in the WCCATD whereas the original JTTR source provided data fields for the blood pressure and temperature variables (See Table A-1).

In light of the clinical practice guidelines, one cannot assume if a physiologic parameter is not documented that it was not done. It would also be unwise to assume if the physiologic measure was not documented that it was not an issue. One can only speculate on the reasons for the amount of missing data, learn what is possible from the data available, and strive to improve data documentation and retrieval methods for the future.

The amount of complete sets of physiologic measures (i.e. all five highest and lowest readings) missing at the leg level were also assessed. The two CCATT transport legs, Leg 3 and Leg 5 had the greatest amount of complete sets of physiologic data missing (See Table 3-5). When complete sets of data are missing, speculation is that complete medical records or flow sheets perhaps were misplaced.

Table 3-5 Complete Missing Data Sets by Leg

Leg	N Missing	Missing %
Leg 1	3	5
Leg 2	23	36
Leg 3	31	48
Leg 4	12	19
Leg 5	34	58

Note: Leg 5 n=61

In an effort to determine if the amount of complete sets of missing data for a leg changed over time, the associations between complete sets of missing data for each leg were assessed by year of injury. A Chi-square test for independence indicated a significant association between complete sets of missing data for Leg 2 and year of injury, $\chi^2 (3, n = 64) = 8.03, p = .046$. The amount of complete sets of missing data for Leg 2 was over 70% (5/7) in 2003 but down to 20% (5/20) in 2005 and 25% (2/6) in 2006. No significant associations were found between year of injury and complete sets of missing data for Leg 3, 4, and 5. Even though not statistically significant, the amount of complete missing data sets for CCATT flights from the AOR to LRMC in 2003 were over 70% (5/2) and 75% (6/2) for CCATT flights from LRMC to CONUS in 2006. These high rates point to a continuing problem of missing CCATT documentation throughout the years reflected in the database.

Obviously the amount of missing data in this database is substantial. It is the only known database, however, that compiles data of this type over a 5 year time frame and includes the entire population of isolated TBI CCATT patients transported from Iraq and Afghanistan. Therefore, it was decided to continue with the study utilizing pairwise deletion when necessary in an effort to begin to explore the occurrence of secondary insults in this new population recognizing the limitations the missing data present.

3.9 Analyses Performed

3.9.1 Demographics

Demographic data were analyzed with descriptive statistics and graphically depicted with histograms, scatterplots, and boxplots. The Kruskal-Wallis Test was chosen to conduct one-way between-groups analysis of variance. This non-parametric test allows scores to be compared on a continuous variable for three or more groups. Scores are converted to ranks and the mean rank for each group is compared (Pallant, 2007). Year was the grouping variable for each of the three dependent variables assessed: days from injury to LRMC, days from injury to CONUS, and the Injury Severity Score.

The Chi-square test for independence is another non-parametric test which was used. In this case, it was used to determine whether two categorical variables, etiology of injury and year of occurrence were related.

3.9.2 Aim 1

Describe the occurrence of secondary insults (hypoxia, hypotension, hyperthermia, hypothermia, and hyperglycemia) in isolated TBI patients transported by CCATTs.

Descriptive statistics were used to address the first aim. By summarizing data in this way, a large mass of unorganized bits of information can be reduced into smaller sets which can describe the original data without sacrificing critical elements (Duffy & Jacobsen, 2005). Occurrence was determined at the person level. A person was considered to have the secondary insult if at any time over the five legs, the secondary insult was identified as having occurred. Therefore, the percent was the number of patients with at least one episode of the secondary insult divided by the total number of patients with measurements recorded at any point for that secondary insult.

Occurrence rates were also calculated by transport leg. Occurrence rates were determined at the person level and calculated by taking the number of patients with at least one recorded episode of the given secondary insult on that leg divided by the number of patients with data for the given physiologic measure on that leg. Therefore, the denominator varied by treatment leg since not all patients had data for all five legs. The denominator also varied by secondary insult due to missing data.

Secondary insults were combined to determine which leg had the greatest occurrence of patients experiencing secondary insults. Occurrence was determined by taking the number of patients with one or more secondary insults for the given leg divided by the number of patients with at least one physiologic measure documented for that leg.

In an attempt to capture repeated legs of secondary insults within a patient, the total number of legs a patient had each secondary insult was determined by creating new variables. A new variable for each secondary insult was created by taking the total number of legs the patient experienced the respective insult. An additional variable was

then created which added the totals for each secondary insult to create a secondary insult total for each patient.

The total number of secondary insults for each patient was assessed at the leg level. Multiple episodes of a given secondary insult during the same leg were counted only once. Patients could have more than one secondary insult documented per leg.

3.9.3 Aim 2

Determine if the occurrence of secondary insults in isolated TBI CCATT patients is associated with extent of injury (ISS), etiology of TBI (blast vs. non-blast injury), type of aircraft used for transport (C-17 vs. C-141), and year of occurrence (from beginning of OIF/OEF to most recent available data).

To address this aim, a logistic regression model was used to analyze the binary occurrence (no=0, yes=1) for each secondary insult as the dependent variable and the predictor variables of extent of injury, etiology of TBI, type of aircraft used for each transport leg, and year of occurrence. Variables were created in the database to align patients with each of the five secondary insults (no=0, yes=1) as well as the top two secondary insult combinations identified in Aim 1. These 7 outcome variables were used to create 7 logistic regression models to examine the association between each of the independent variables with the occurrence of the secondary insult(s).

The first step in conducting the logistic regression was assessing the assumptions. A large number of predictors can result in convergence problems if the sample size is small – a concern for this study. This problem is further intensified when predictors are categorical with limited cases in each category. Since the sample is not large and the predictors are categorical with limited cases in some categories, the number of predictors

was reduced. To determine which predictors to eliminate, bivariate correlations were assessed. Kendall's tau correlation was chosen since it accommodates non-parametric data and is recommended for small data sets with a large number of tied ranks (Field, 2005). Assessment of correlations between predictor variables revealed a positive correlation between aircraft used from AOR to LRMC, aircraft used from LRMC to CONUS, and year of occurrence in all directions (See Table A-4). Since all three of these predictor variables were correlated with each other, year of occurrence and aircraft used from AOR to LRMC were chosen for the model and the aircraft used from LRMC to CONUS was not included in the models. The remaining factors resulted in four predictor variables for a maximum sample size of 64.

A review of both the correlation matrix and collinearity statistics (See Table A-5) shows a lack of intercorrelation among predictor variables, which is desirable. Bivariate correlations are all less than 0.7. Collinearity statistics can pick up problems with multicollinearity that may not be evident in the correlation matrix. Tolerance values above 0.1 and VIF values below 10 are desired to further support a lack of multicollinearity (Pallant, 2007).

The Chi-square test for independence was used to further explore the relationship between variables for this aim. The Fisher's Exact Test was used for 2 by 2 tables with small cell frequencies.

Chapter 4: Findings

4.1 Overview

This chapter presents the findings from the analyses performed. It begins with demographic descriptions followed by each aim.

4.2 Demographics

A demographic overview of the study participants can be seen in Table 4-1. The mean age of patients in this study was 27 years with almost 70 percent of the sample serving in the Army. Gender was not included in the demographic data since all but one of the study patients were male. Race was not specified since it was not available in the primary database. The mean Injury Severity Score (ISS) was 17; scores greater than 15 indicate severe injury. Over half of the injuries were caused by blasts. Even though the primary database encompasses the time period from October of 2001 through May 2006, the earliest isolated TBI patient used for this study was injured December 2002. Most of the patients in this study were injured in 2004 and 2005. Days from injury to LRMC and to CONUS are both positively skewed (See Table A-3) with an average time in days from the point of injury to arriving at LRMC of 2.3. The mean time from point of injury to arrival in CONUS was 6.8 days. The disposition from the first CONUS hospital is unknown for almost half of the study participants. Approximately one quarter of the study patients was transferred to another inpatient treatment facility, 13 % were discharged home or to outpatient treatment, and 8 % were reported to have died.

Table 4-1 Demographic Characteristics of Isolated TBI CCATT Patients (n=64)

Characteristic		Mean \pm SD or N (%)	Range
Age		27 \pm 8	18 - 59
Service Branch	Army	44 (69)	
	Marine Corp	12 (19)	
	Air Force	1 (2)	
	Navy	1 (2)	
	Civilian	4 (6)	
	Other	2 (3)	
Injury Severity Score (n=59)		17 \pm 8	1 - 35
Glasgow Coma Scale (n=61)		10.6 \pm 4.4	3 - 15
Glasgow Coma Scale Motor (n=57)		4.7 \pm 1.8	1 - 6
Mechanism of Injury	Blast	34 (53)	
	Penetrating	16 (25)	
	Blunt	13 (20)	
	Heat Stroke	1 (2)	
Year of Injury	2003	7 (11)	
	2004	24 (38)	
	2005	25 (39)	
	2006	8 (13)	
Days from Injury to LRMC Arrival (n=56)		2.3 \pm 2.2	1 - 11
Days from Injury to CONUS Arrival (n=43)		6.8 \pm 4.3	2 - 23
Disposition	Discharged	8 (13)	
	Transferred	17 (27)	
	Died	5 (8)	
	Transported by other AE	3 (5)	
	Unknown	31 (48)	

LRMC – Landstuhl Regional Medical Center; CONUS – Contiguous United States; AE – Air medical Evacuation

The primary aircraft used for CCATT transports from 2001 to 2006 were the C-141 and the C-17. Table 4-2 shows the distribution of aircraft used to transport CCATT patients in this study. There was approximately an equal distribution of C-141 and C-17 aircraft used for both the transports from AOR to LRMC and from LRMC to CONUS.

Table 4-2 Aircraft Used by CCATT to Transport Isolated TBI Patients

Characteristic	C-17	C-141
	N (%)	N (%)
AOR to LRMC (n=60)	28 (47)	32 (53)
LRMC to CONUS (n=36)	16 (44)	20 (56)

AOR – Military Area of Responsibility; LRMC – Landstuhl Regional Medical Center; CONUS – Contiguous United States

Table 4-3 depicts the results of the Kruskal-Wallis Test where year was the grouping variable for each of the dependent variables assessed: days from injury to LRMC, days from injury to CONUS, Injury Severity Score, Glogsgow Coma Scale score, and age.

A statistically significant difference in days from injury to arrival at LRMC was seen across the years within the database (Gp1, n=6: 2003, Gp2, n=20: 2004, Gp3, n=23: 2005, Gp4, n=7: 2006), $\chi^2(3, n=56) = 19.1, p < .001$. The 2004 year group had the highest median score ($Md = 2.5$) whereas both the 2005 and 2006 year groups had a median of 1.0 day from injury to arrival at LRMC with no variation in 2006. This is depicted graphically by box plots in Figure 4-1.

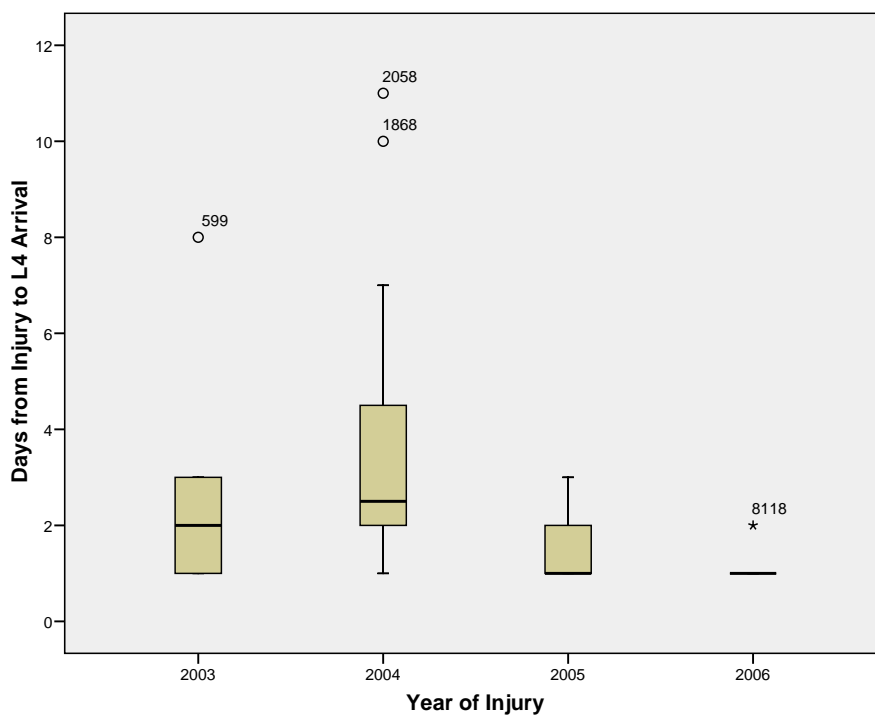


Figure 4-1 Box Plots of Days from Injury to LRMC Arrival by Year

The days from injury to arrival in CONUS was also statistically significant across the years within the database (Gp1, n=3: 2003, Gp2, n=17: 2004, Gp3, n=19: 2005, Gp4, n=4: 2006), $\chi^2(3, n=43) = 18.5, p < .001$. The most recent year, 2006, had the shortest median time with 3.5 days from point of injury to arrival in CONUS whereas both the 2003 and 2004 year groups had a median days from injury to CONUS arrival of 8 days. This can also be seen in the box plots shown in Figure 4-2.

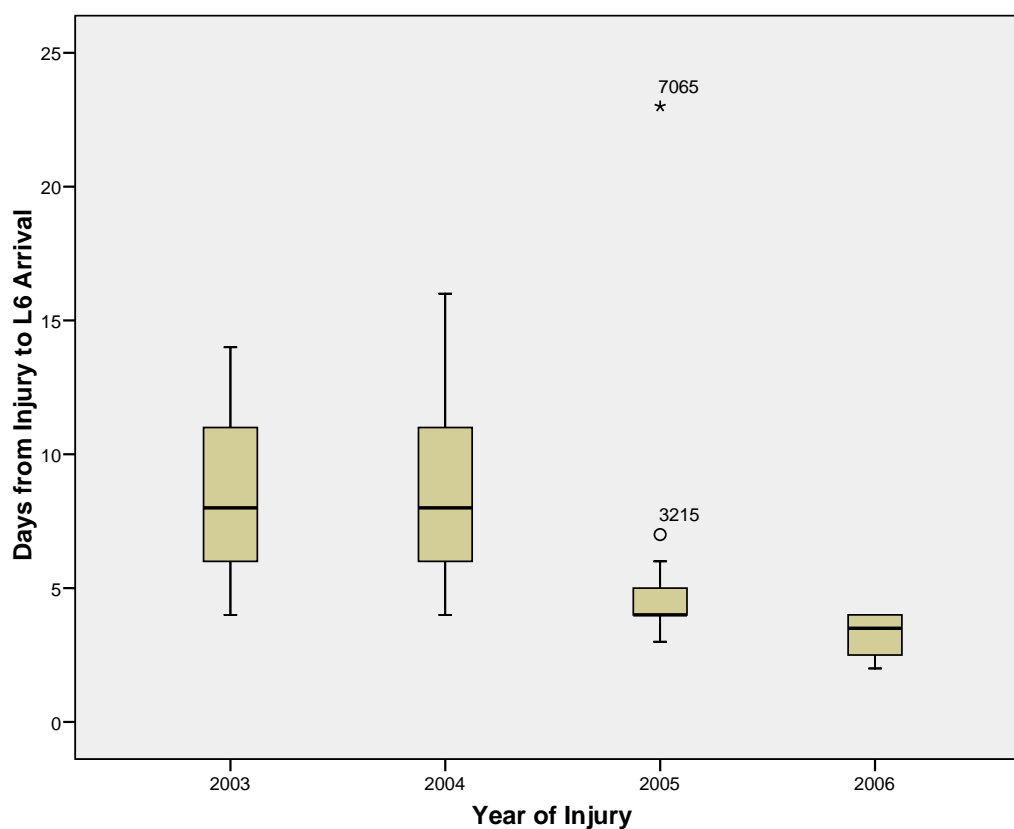


Figure 4-2 Box Plots of Days from Injury to CONUS Arrival by Year

Neither the Injury Severity Score nor the initial Glasgow Coma Scale score were statistically significant by years within the database suggesting consistent severity across years. Values for ISS were (Gp1, n=5: 2003, Gp2, n=22: 2004, Gp3, n=24: 2005, Gp4, n=8: 2006), χ^2 (3, n=59) = 4.2, $p=.24$ and for GCS were (Gp1, n=6: 2003, Gp2, n=22: 2004, Gp3, n=25: 2005, Gp4, n=8: 2006), χ^2 (3, n=61) = 4.0, $p=.26$. The median ISS for 2003 was 9 but ranged from 17 to 18.5 for years 2004 – 2006; whereas the median GCS for 2003 was 6.5 and ranged from 10 to 14 for 2004 – 2006.

Age was not statistically significant across years within the database with injured patients consistently young (Gp1, n=7: 2003, Gp2, n=24: 2004, Gp3, n=25, Gp4, n=8: 2006), χ^2 (3, n=64) = 3.4, $p=.34$. The median age ranged from 22 to 28 years.

Table 4-3 Time from Injury, Injury Severity, and Age Variables by Year

Dependent Variables	N	χ^2	df	p	Total Median
Days from Injury to LRMC	56	19.1	3	<.001	2.0
Days from Injury to CONUS	43	18.5	3	<.001	5.0
Injury Severity Score	59	4.2	3	.241	17
Glasgow Coma Scale	61	4.2	3	.263	12
Age	64	3.4	3	.335	24

LRMC – Landstuhl Regional Medical Center; CONUS – Contiguous United States

The association between etiology of injury (blast vs. non-blast) and the year of injury was also assessed. A Chi-square test for independence indicated no significant association between etiology of injury and the year of injury, χ^2 (3, n=64) = 1.94, $p = .59$, Cramer's V = .17. Of note, however, is the violation of the assumption of minimum expected cell frequency. Sixty-three percent (5/8) of the cells had expected frequencies

of five or more which is less than the minimum recommended of at least 80 percent of cells having expected frequencies of five or more.

The relationship between ISS and GCS was explored since they are both commonly used as indicators of severity of injury. ISS and GCS were recoded into categorical variables with their resulting frequencies shown in Table 4-4. The greatest frequencies of patients were found in the more severe ISS categories whereas the greatest frequency of patients was classified by the GCS as mild.

Table 4-4 Injury Severity Score (ISS) and Glasgow Coma Scale (GCS) by Categories

Category	Frequency	Percent
Injury Severity Score (n=59)		
Minor	11	18.5
Moderate	12	20.5
Moderate/Severe	18	30.5
Severe/Critical	18	30.5
Glasgow Coma Scale (n=61)		
Mild	25	41.0
Moderate	16	26.2
Severe	20	32.8

The motor component of the GCS has been used as a marker of the overall GCS especially in the acute period of a critically ill or injured patient who may not be able to talk due to tracheal intubation or able to open eyes due to injury or swelling. Fifty-five patients had documentation of both an initial GCS score and the motor component score. As would be expected, the continuous values of the initial GCS and motor component of the GCS were highly correlated, $r=.79$, $n=55$, $p<.001$. Since these variables have a large correlation, the initial GCS will be used for further analyses.

Even though ISS and GCS both are indicators of severity of illness, when these categorical variables (e.g. GCS 3 level and ISS 4 level) were examined for association,

no statistically significant relationship was found. A Chi-square test for independence indicated no significant association between ISS and GCS, $\chi^2 (6, n=57) = 7.34, p = .29$. This might be expected with the higher frequency of mild GCS scores. GCS scores were those first recorded and may have reflected patient status prior to neurological deterioration.

4.3 Aim 1

Describe the occurrence of secondary insults (hypoxia, hypotension, hyperthermia, hypothermia, and hyperglycemia) in TBI patients transported by CCATTs.

Hyperthermia was the secondary insult identified most frequently with almost half of the study participants having documented temperatures of over 38.5°C. A quarter of the patients with recorded SpO₂ readings had documented hypoxia and 17 % of patients with documented systolic blood pressures were hypotensive. Hypothermia was the secondary insult identified least often. Over half of the study participants had at least one documented episode of a secondary insult (See Table 4-5).

Table 4-5 Occurrence of Secondary Insults in Isolated TBI CCATT Patients

Secondary Insult	Pts with Insult/Total Pts	%
Hyperthermia	29/62	47
Hypoxia	13/51	25
Hypotension	11/64	17
Hyperglycemia	6/47	13
Hypothermia	5/62	8
None	30/64	47

Note: Percentages are greater than 100 since patients may have more than one secondary insult.

When occurrence of secondary insults was assessed by leg, the period of time at the AOR medical treatment facility (Leg 2) was the leg with the greatest percentage of patients with documented secondary insults. The lowest percentage of patients with

documented secondary insults occurred during the CCATT flight from the AOR MTF to LRMC (See Figure 4-3).

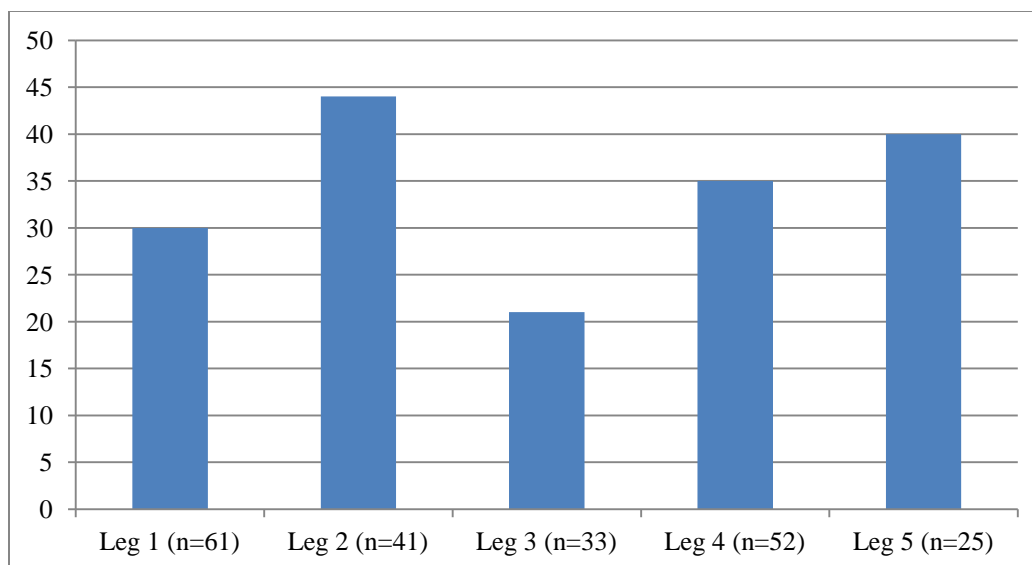
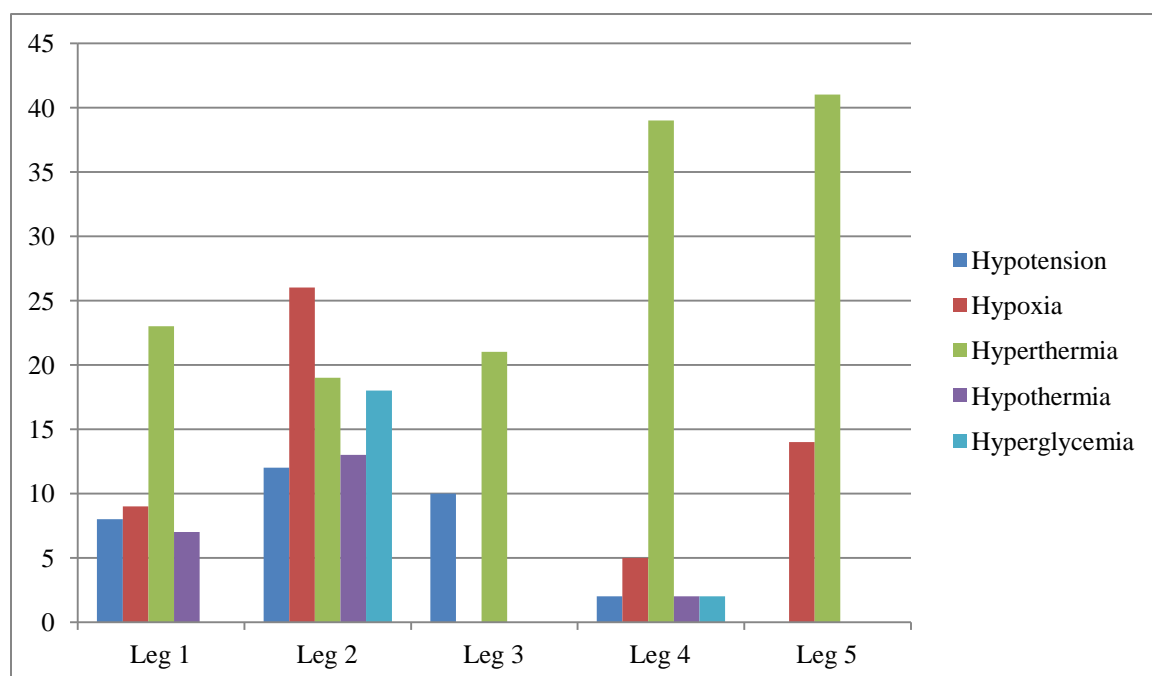


Figure 4-3 Percent of Study Patients with One or More Secondary Insults by Leg

Hyperthermia was the secondary insulted with the greatest rate of occurrence for all legs except Leg 2 ranging from 21 to 41 percent. Hyperthermia was the only secondary insult that continually increased in occurrence rate over legs 2, 3, 4, and 5. Hypoxia occurred at a greater rate than hyperthermia during Leg 2 with a rate of 26 percent. Hypotension and hyperthermia were the only secondary insults documented for CCATT flights from the AOR to LRMC whereas hypoxia and hyperthermia were the only secondary insults documented for CCATT flights from LRMC to CONUS (See Table 4-6 and Figure 4-4).

Table 4-6 Occurrence of Secondary Insults in Isolated TBI CCATT Patients by Leg

Secondary Insult	Leg 1 With/Total (%)	Leg 2 With/Total (%)	Leg 3 With/Total (%)	Leg 4 With/Total (%)	Leg 5 With/Total (%)
Hypotension	5/60 (8)	4/34 (12)	3/31 (10)	1/44 (2)	0/24
Hypoxia	1/11 (9)	9/35 (26)	0/30	2/40 (5)	3/22 (14)
Hyperthermia	13/56 (23)	6/31 (19)	5/24 (21)	17/44 (39)	7/17 (41)
Hypothermia	4/56 (7)	4/31 (13)	0/24	1/43 (2)	0/17
Hyperglycemia	0/7	5/28 (18)	0/6	1/41 (2)	0/4

**Figure 4-4** Percent of Study Patients with Secondary Insults by Leg

No patients had any given secondary insult documented for all five legs.

Hyperthermia was most often documented on multiple legs where hyperglycemia had no patients with documented hyperglycemia on more than one leg (See Table 4-7).

Table 4-7 Number of Legs with Secondary Insults in Study Patients

Secondary Insult	0 Legs #(%)	1 Leg #(%)	2 Legs #(%)	3 Legs #(%)	4 Legs #(%)	5 Legs #(%)
Hypotension (n=64)	53 (83)	9 (14)	2 (3)	0	0	0
Hypoxia (n=51)	38 (75)	12 (24)	0	1 (2)	0	0
Hyperthermia (n=62)	33 (53)	15 (24)	10 (16)	3 (5)	1 (2)	0
Hypothermia (n=62)	57 (92)	2 (3)	2 (3)	1 (2)	0	0
Hyperglycemia (n=47)	41 (87)	6 (13)	0	0	0	0

Note: Percents do not add up to 100 due to rounding.

The total number of secondary insults a patient had documented ranged from 0 to 7. Secondary insults were experienced by over one half of the study participants. Close to 20 percent had only one secondary insult on one leg documented whereas over one third of the study participants had either multiple secondary insults and/or multiple legs of documented secondary insults.

Previous studies have reported worse outcomes for patients with a combination of secondary insults. Therefore, combinations of secondary insults were explored. Twenty patients had documented combinations of secondary insults. Hyperthermia was a secondary insult in each of these combinations. The combination of hyperthermia and hypoxia as well as hyperthermia and hypotension were the most common combinations documented each representing 25 percent of the secondary insult combinations (See Table 4-8). Of the six patients with three or more different secondary insults, disposition status was not available for four, one was transferred to another inpatient facility, and one was discharged on convalescent leave.

Table 4-8 Frequencies of Secondary Insult Combinations (n=20)

Secondary Insults	#	%
Hyperthermia, Hypoxia	5	25
Hyperthermia, Hypotension	5	25
Hyperthermia, Hyperglycemia	3	15
Hyperthermia, Hypoxia, Hypotension	1	5
Hyperthermia, Hypoxia, Hypotension, Hypothermia	1	5
Hyperthermia, Hypoxia, Hypotension, Hyperglycemia	1	5
Hyperthermia, Hypoxia, Hypotension, Hypothermia, Hyperglycemia	1	5
Hyperthermia, Hypoxia, Hypothermia	1	5
Hyperthermia, Hypotension, Hypothermia	1	5
Hyperthermia, Hypothermia	1	5

4.4 Aim 2

Determine if the occurrence of secondary insults in isolated TBI CCATT patients is associated with extent of injury (ISS), etiology of TBI (blast vs. non-blast injury), type of aircraft used for transport (C-17 vs. C-141), and year of occurrence (from beginning of OIF/OEF to most recent available data).

An analysis of the five individual secondary insult and two secondary insult combination logistic regression models indicated the models with dependent variables of hyperglycemia and the secondary insult combinations did not converge. The model with hyperthermia as the dependent variable was the only model which yielded a statistically significant model coefficient (See Table 4-9).

Table 4-9 Logistic Regression Model Summaries Predicting Secondary Insults

Model DV	N	Omnibus	of	Model	Model	Summary
		Test	Model	Coefficients	Cox & Snell R ²	Nagelkerke R ²
		Chi-Square	df	Sig.		
Hyperthermia	53	14.85	4	.005	.24	.33
Hypotension	55	7.43	4	.115	.13	.21
Hypoxia	45	4.35	4	.361	.09	.14
Hypothermia	53	1.22	4	.876	.02	.05

Note: Hyperglycemia and secondary insult combination models did not converge.

The models contained four independent variables: injury severity score (ISS), blast vs. non-blast injury, year of injury occurrence, and the aircraft used for transport from the AOR to LRMC. The full model with hyperthermia as the dependent variable was statistically significant, $\chi^2(4, N=53) = 14.85, p < .01$, indicating the model was able to distinguish between patients who did develop hyperthermia and those who did not. The model as a whole explained between 24% (Cox and Snell R squared) and 33% (Nagelkerke R squared) of the variance in the development of hyperthermia, and correctly classified 71.7% of the cases. As shown in Table 4-10, only one of the independent variables made a unique statistically significant contribution to the model (ISS). The odds ratio of 1.16 for ISS indicates that for every one point increase in ISS, patients were 1.16 times more likely to have documented hyperthermia, controlling for other factors in the model. Details of the non-statistically significant models can be found in the appendix (See Tables A-6, A-7, A-8).

Table 4-10 Logistic Regression Predicting Likelihood of Documented Hyperthermia (n=53)

Variable	B	S.E.	Wald	df	p	Odds Ratio	95% CI Lower	95% CI Upper
ISS	.15	.05	9.91	1	.002	1.16	1.06	1.27
Blast vs. Non-Blast	.50	.67	.56	1	.455	1.65	.45	6.06
Year of Injury	.71	.58	1.50	1	.221	2.03	.65	6.31
Aircraft for Leg 3	-.65	.81	.63	1	.428	.53	.11	2.58
Constant	-3.99	1.38	8.33	1	.004	.02		

ISS – Injury Severity Score

Even though the analysis above suggests little association between secondary insults and variables studied, further assessment was conducted to get a clearer picture of secondary insults in this patient population.

4.4.1 Extent of Injury

With the lack of association found earlier between ISS and GCS, regression models were reassessed with GCS for indicator of injury rather than ISS. With independent variables of GCS, blast versus non-blast etiology, year of occurrence, and aircraft used from AOR to LRMC, no models were found to be significant (See Table 4.11).

Table 4-11 GCS Logistic Regression Model Summaries Predicting Secondary Insults

Model DV	N	Omnibus Test	of	Model Coefficients	Model	Summary
		Chi-Square	df	Sig.	Cox & Snell R ²	Nagelkerke R ²
Hypotension	57	8.23	4	.084	.13	.22
Hypoxia	48	5.09	4	.278	.10	.15
Hyperthermia	55	4.44	4	.350	.08	.10
Hypothermia	55	1.79	4	.774	.03	.07

GCS – Glasgow Coma Scale; DV – Dependent Variable

Note: Hyperglycemia and secondary insult combination models did not converge.

Even though GCS was not a predictor of secondary insults, it may be a better indication of disposition. Sample size and cell counts do not allow statistical analysis but all five documented cases of death had initial GCS scores within the severe range. Of the seven cases with discharge, convalescent leave, or transfer to an outpatient facility documented as disposition, six had initial GCS scores in the mild range and one in the moderate range. The ISS demonstrates more variability. Of the five documented cases of death, three had ISS in the critical range but one was in the minor range and one in the moderate range. Of the six patients with discharge, convalescent leave, or transfer to an outpatient facility documented as disposition, two had ISSs in the critical range, two in the severe range, one in the moderate range, and one patient was classified as minor.

Of the five patients with documented death as the disposition, three died at LRMC and two died after returning to CONUS. Ages ranged from 19 to 41 and injury severity scores ranged from 4 to 29. All years of the database were included. Two of the patients' injuries were the result of penetrating blast injuries, one was the result of a closed non-blast injury from a motor vehicle crash, and two were penetrating non-blast injuries one from a motor vehicle crash and one from a gunshot wound. Three of the patients had multiple secondary insults documented. The two patients with no documented secondary insults had no physiologic measures recorded for Legs 2 or 3 and missing measures for Legs 1, 4, and 5. The most common secondary insult recorded was hyperthermia which was found in 3 of 4 patients with temperature readings recorded.

4.4.1.1 ICP and CPP

Joint Theater Trauma System clinical practice guidelines for severe head trauma recommend ICP monitoring for TBI patients with a GCS score of 3-8 with an abnormal CT scan or if two or more of the following adverse features are present in a patient with severe head injury and a normal head CT scan: age > 40 yr, unilateral or bilateral motor posturing, SBP < 90 mm Hg (Bridges, 2009). A subgroup analysis of patients with ICP monitoring documented was conducted. Thirty-five patients had at least one ICP reading documented whereas 29 had at least one documented CPP reading. Table 4-12 shows the frequency of patients with at least one ICP greater than 20 mm Hg as well as patients with at least one CPP less than 60 mm Hg.

Table 4-12 Frequency of Patients with Abnormal ICP and CPP Values

Category	Frequency	Percent
ICP (n=35)		
No ICP > 20 mmHg	17	49
ICP > 20 mmHg	18	51
CPP (n=29)		
No CPP < 60 mmHg	14	48
CPP < 60 mmHg	15	52

ICP – Intracranial Pressure; CPP – Cerebral Perfusion Pressure

As would be expected, ICP and CPP had a strong negative correlation with the exception of Leg 5 (See Table 4-13). Of the nine Leg 5 cases with both ICP and CPP, all CPP values were less than 60 mm Hg and two cases had ICP values greater than 20 mm Hg. Since it is the ICP with the abnormal values in Leg 5, fewer cases of CPP documented, and the large correlations between ICP and CPP in Legs 2-4, ICP will be used for further analyses.

Table 4-13 Correlations between ICP and CPP by Legs

Variables	<i>r</i>	N	<i>p</i>
Leg 2 ICP x Leg 2 CPP	-.62	20	.004
Leg 3 ICP x Leg 3 CPP	-.77	14	.001
Leg 4 ICP x Leg 4 CPP	-.64	20	.002
Leg 5 ICP x Leg 5 CPP	-.58	9	.104

ICP – Intracranial Pressure; CPP – Cerebral Perfusion Pressure

Note: No cases of CPP documented during Leg 1

A Chi-square test for independence indicated no significant association between the three categories of GCS and occurrence of elevated ICP (yes/no), $\chi^2 (2, n=34) = 5.26$, $p = .07$. Even though no statistical significance was found, over 76% of the patients who had ICP monitoring had GCS classifications of moderate or severe. Statistical analysis of ISS and the occurrence of elevated ICP was not conducted due to zero cell size. Review of the crosstabulation, however, revealed 79% of the patients with ICP monitoring had

ISS classification of severe or critical and only 6% had ISS designated as minor.

Seventeen cases had documented disposition and ICP monitoring. When the crosstabulation of ICP (yes/no) and disposition (three categories) was examined, all five documented cases of death had ICPs of greater than 20 mmHg. There were no documented cases of elevated ICP who were discharged, on convalescent leave, or transported to an outpatient facility.

Only one statistically significant association was found between elevated ICP and the occurrence of secondary insults (See Table 4-14). A chi-square test for independence indicated a significant association between elevated ICP and the occurrence of hypotension, $\chi^2 (1, n=35) = 5.4, p = .04$. Over 87% of the patients with hypotension had elevated ICP whereas 94% of the patients without elevated ICP did not have hypotension.

Table 4-14 Associations between Occurrence of Elevated ICP and Secondary Insults

Secondary Insults	N	χ^2	df	p	Phi
Hypotension*	35	5.40	1	.04	.39
Hypoxia	31	0.00	1	.98	.00
Hyperthermia	34	0.13	1	.71	.06
Hypothermia*	34	1.13	1	.60	.18
Hyperglycemia*	26	0.01	1	.99	-.02

* Fisher's Exact Test

4.4.2 Etiology of TBI

No significant association was found in the model above between secondary insults and whether the injury was caused by a blast or non-blast injury. Blast injuries were those injuries caused by an explosive blast. Non-blast injuries were those as a result of non-blast causes such as gunshot wounds, motor vehicle crashes, or falls. Both blast and non-blast injuries can result in either closed or penetrating head injuries. Therefore,

further assessment was conducted with each category of blast and non-blast injuries separated into closed or penetrating head injuries (See Table 4-15 and Figure 4-5).

Table 4-15 Injury Etiology of Study Participants (n=64)

Etiology	Frequency	Percent
Non-Blast Closed	13	20
Non-Blast Penetrating	16	25
Blast Closed	12	19
Blast Penetrating	23	36

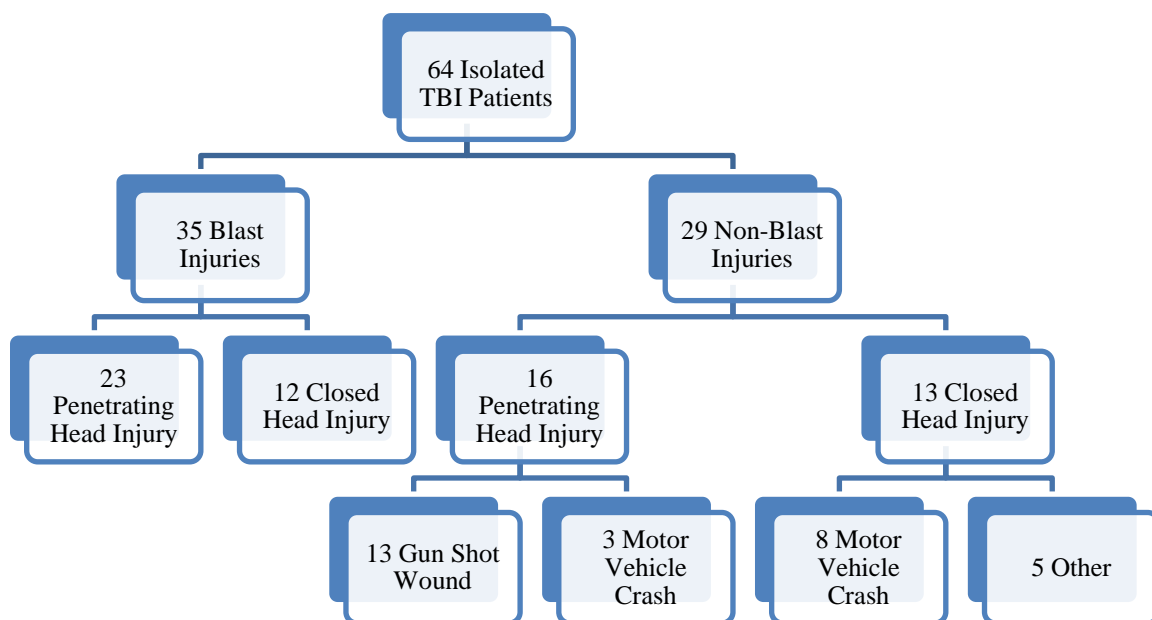


Figure 4.5 Diagram of Etiology Breakdown of Study Patients

This expanded etiology was used to assess associations with the secondary insults of hypotension, hypoxia, and hyperthermia even though some of the cell counts were small. Hypothermia and hyperglycemia were not analyzed due to cell counts of zero. None of the secondary insults assessed showed a significant association with the expanded etiology of injury (See Table 4-16).

Table 4-16 Associations between Etiology and Secondary Insults (likelihood ratio)

Secondary Insults	N	χ^2	df	p	Cramer's V
Hypotension	64	1.34	3	.72	.14
Hypoxia	51	4.47	3	.22	.30
Hyperthermia	62	5.43	3	.14	.29

Note: Hypothermia and Hyperglycemia not included due to zero cell count.

4.4.3 Type of Aircraft

The type of aircraft used for transport from the AOR to LRMC was not shown to have a significant association with the occurrence of documented secondary insults in the logistic regression model above. A significant association was found, however, between the type of aircraft and the secondary insults of hypotension and hypoxia (See Table 4-17).

Table 4-17 Associations between Aircraft used for AOR to LRMC Transport and Secondary Insults

Secondary Insults	N	χ^2	df	p	Cramer's V
Hypotension	60	4.39	1	.05	.27
Hypoxia*	49	5.02	1	.04	.32
Hyperthermia	58	0.69	1	.41	.11
Hypothermia*	58	0.09	1	1.00	.04

* Fisher's Exact Test for significance

Note: Hyperglycemia not included due to zero cell count.

The association between the aircraft used for the CCATT transport from LRMC to CONUS and the documented occurrence of secondary insults was also assessed. There were no statistically significant differences between the types of aircraft used and the documented occurrence of any of the secondary insults assessed (See Table 4-18).

Table 4-18 Associations between Aircraft used for LRMC to CONUS Transport and Secondary Insults

Secondary Insults	N	χ^2	df	p	Cramer's V
Hypotension*	36	3.20	1	.10	.30
Hypoxia*	28	0.87	1	.43	.18
Hyperthermia	35	0.01	1	.92	.02
Hypothermia*	35	0.03	1	1.00	.03
Hyperglycemia*	26	0.25	1	1.00	.10

* Fisher's Exact Test for significance

4.4.4 Year of Occurrence

To further explore any changes in documented secondary insults over the four years of the database, crosstabulations and Chi-Square tests were conducted. No statistically significant differences between the documented occurrences of hypoxia and hyperthermia over the four year time period were found (See Table 4-19). Hypotension, hypothermia, and hyperglycemia were not included in the Chi-Square tests due to cell counts of zero.

Table 4-19 Associations between Year of Injury and Secondary Insults*

Secondary Insults	N	χ^2	df	p	Cramer's V
Hypoxia	51	0.62	3	.89	.11
Hyperthermia	62	1.48	3	.68	.15

* Likelihood Ratio used.

Note: Hypotension, Hypothermia, and Hyperglycemia not included due to zero cell count.

4.5 Summary of Findings

In summary, there are five major findings of note in this chapter. The first is the decrease in median days from the point of injury to patients arriving in Germany (2.5 to 1 day) and in the United States (8 to 3.5 days) over the course of the database. Second, over half of the study participants had at least one documented episode of a secondary insult. Hyperthermia was the secondary insult found most commonly with the

occurrence rate increasing from the point of injury to arrival in the United States. All other secondary insults assessed had the greatest occurrence rates documented while the patients were still in the AOR. No significant differences in the documented occurrence of secondary insults were found between type of aircraft used for CCATT transport even with the primary aircraft changing over the course of the database. Finally, no significant differences in the documented occurrence of secondary insults were found by year of occurrence even with the time from injury to arrival in Germany and in the United States decreasing.

Chapter 5: Discussion, Implications, and Recommendations

5.1 Overview

The results of the study are discussed in this chapter beginning with the demographic characteristics followed by each aim. Strengths of the study are recognized and limitations are acknowledged. The chapter finishes with a discussion of the implications of the study.

5.2 Demographic Characteristics

The demographic picture of a study participant is one of a male Army soldier in his 20s with a fairly equal chance of being injured by a blast or a non-blast cause. This profile is consistent with previous studies. Arthurs et al. (2006) described their sample of 2,848 combat trauma troops as being 97 percent male, 65 percent US or Coalition troops with a mean age of 28 and 37 percent with wounds as a result of blast fragments. A study of 133 combat CCATT patients showed a similar picture. The mean age of trauma patients was 27 years, 92 percent were male, and 91 percent of the trauma patients were US military (Mason, Eadie & Holder, 2009). No significant differences in age or etiology of injury (blast vs. non-blast) were found over the four years of study data.

ISS was designed for patients with multisystem injuries but was utilized in this isolated TBI sample in an effort to compare severity of injuries across studies. The mean and median ISS identified were both 17, greater than 15 the recognized point indicating severe injury. In a study of military TBI and spinal column injured casualties that included polytrauma patients, the average ISS was 30 and the mean admission GCS to the United States was 11 (Bell et al., 2009). The higher ISS level is not surprising given the inclusion of polytrauma patients in their sample. Bell et al. found a statistically

significant relationship between GCS and ISS whereas no association was found between the two in our current study. The initial GCS also supports the severe nature of injuries with the median first recorded GCS score of 12. This value falls near the top end of the moderate severity category. The severity of injury is not surprising since the sample is of CCATT patients who are patients requiring critical care. An ISS of 17 falls between the mean score of 14 found by Arthurs et al. (2006) in their sample of combat trauma troops and an ISS of 20 found in a CCATT study of shorter duration (Mason, Eadie & Holder, 2009). The injury severity as documented by the ISS did not change significantly over the four years encompassed in the study.

Over the four year period between 2003 through 2006, the amount of days from the point of injury to arriving at LRMC decreased from a median of 2.5 days to 1 day. This is consistent with other reports which state an average of 28 hours from the point of injury until being evacuated to Germany by CCATT (Johannigman, 2008). Other studies report a median time from the point of wounding to arriving at a tertiary hospital in CONUS to be 8.5 days (Fox et al., 2005). This study found the median days from injury to CONUS to be 8 days in 2003 and 2004 but down to 3.5 days by 2006. .

5.3 Aim 1

Describe the occurrence of secondary insults (hypoxia, hypotension, hyperthermia, hypothermia, and hyperglycemia) in TBI patients transported by CCATTs.

The documented occurrences of the secondary insults examined in this study are similar to occurrence rates found in civilian studies (See Table 5-1). This similarity in occurrence rates, however, needs to be considered in light of the missing data. Even though occurrence is based only on patients for whom the physiologic measures were

recorded, given the austere environment and critical nature of the patients, secondary insults may have occurred which were not recorded.

Table 5-1 Comparison of Secondary Insult Occurrence Rates between Studies

Secondary Insult	This Study Occurrence (%)	Literature Occurrence (%)	Review Study Period
Hyperthermia	47	73	Stocchetti et al., 2002
		33	Diringer et al., 2004
		25	Jiang et al., 2002
Hypoxia	25	57	Stocchetti et al., 1996
		46	Jeremitsky et al., 2003
		35	Miller et al., 1982
		25	Chi et al., 2006
		20	McHugh et al., 2007
Hypotension	17	11	Jiang et al., 2002
		68	Jeremitsky et al., 2003
		35	Chestnut et al., 1993a
		32	Chestnut et al., 1993b
		20	Stocchetti et al., 1996
		18	McHugh et al., 2007
		15	Miller et al., 1982
Hyperglycemia	13	9	Chi et al., 2006
		3	Shafi & Gentilello, 2005
		48	Young et al., 1989
		42	Jeremitsky et al., 2003
Hypothermia	8	33	Lam et al., 1991
		26	Jeremitsky et al., 2003
		18	Arthurs et al., 2006
		10	McHugh et al., 2007
		9	Shafi et al., 2005
		5	Wang et al., 2005

ICU – Intensive Care Unit; ED – Emergency Department

Hyperthermia is common in critically ill TBI patients and can be a result of posttraumatic cerebral inflammation, direct hypothalamic damage, or secondary infection (Thompson, Tkacs, Saatman, Raghupathi & McIntosh, 2002). Fever after a TBI is likely related to both the development of infection and some degree of hypothalamic dysfunction from the injury (Badjatia, 2009). Increases in temperature within the first 24

hours after brain injury are often attributed to diffuse mechanisms such as sympathetic tone and inflammation. Fever, however, when associated with infection can enhance the body's ability to fight infection providing a beneficial effect. Therefore, the approach to managing fevers should be a balance between limiting secondary injury and impairing the ability to fight infection (Badjatia, 2009). The greatest risk of secondary injury from hyperthermia is usually limited to the early phase in the course of most acute insults whereas the risk of infection increases with time. The priority then should be to aggressively control fever during the first few days following head injury. Fever control beyond this time periods is less likely to be helpful and may even be detrimental (Badjatia, 2009). Hyperthermia was the secondary insult found most commonly in this study. The occurrence rate of 47%, however, is far less than the 73% found by Stocchetti et al. (2002) in their study of hyperthermia the first week post trauma of TBI patients. Hyperthermia was the only secondary insult whose occurrence rates increased over the course of the study legs. This is not surprising given the contaminated wartime environment especially from secondary blast injuries propelling fragments and debris resulting in penetrating injuries. With the increasing likelihood of the cause of hyperthermia being from infection as the time from injury increases, those patients with hyperthermia early on should be targeted for normothermic measures. Antipyretic agents rely on intact thermoregulation and may not be effective in patients with neurogenic injury (Badjatia, 2009). Limitations in electricity, weight, and safety need to be considered when nonpharmacologic measures for the treatment of hyperthermia in military field and cargo aircraft transport environments are explored (Bridges, 2007).

The occurrence rate of hypoxia documented in this study was consistent with hypoxia reported in civilian studies (See Table 2-7). Hypoxia was documented most commonly during Leg 2, which is consistent with the acute phase reported in the literature. Only one patient in this study was documented to have more than one leg of hypoxia suggesting ease of oxygenation even in the austere wartime environments. Unreported hypoxic events could be another possible explanation for the low rate of hypoxia reoccurrence. Where there were no documented cases of hypoxia during the CCATT flights from the AOR to LRMC, 14% of the patients with SpO₂ recorded during the CCATT flights from LRMC to CONUS did have hypoxic levels recorded. Therefore, CCAT teams should remain ever vigilant of the oxygenation status of their patients even if the patients have had no previous hypoxic episodes.

Hypotension was documented to have occurred in 17 % of the study patients. This is consistent with previous research which reported occurrence rates of hypotension from 3 to 68 % (See Table 2-7). Leg 2, the period of time at the AOR medical treatment facility, was the leg with the greatest documented occurrence of hypotension. Hypotension occurred during more than one leg for only two patients. Care should be taken when surmising whether this lack of repeated hypotension is because of rapid control of declining systolic blood pressure or a result of underreported events. Whereas the CCATT flights from LRMC to CONUS only had secondary insults of hyperthermia and hypoxia documented, the CCATT flights from the AOR to LRMC only had secondary insults of hypotension and hyperthermia documented. Three of the 31 Leg 3 patients with documented systolic blood pressures had reported episodes of hypotension.

As with hypoxia, CCAT teams should be on the lookout for impending hypotension in an effort to prevent this secondary insult from occurring.

Hyperglycemia is thought to exacerbate secondary brain injury in TBI patients. The process by which hyperglycemia exacerbates secondary brain injury is unclear but may include hyperosmolarity, lactic acid production, alterations in neuronal pH, and increases in excitatory amino acids (Jeremitsky, Omert, Dunham, Wilberger & Rodrigues, 2005). Single-channel point-of-care glucose monitors such as the *i-STAT* (Abbott) have been approved for flight and far forward operating areas so that blood glucose levels can be monitored even in the austere wartime environments if the equipment is available and a clinical need is identified (Bridges, 2009). Even so, blood glucose testing outside the hospital environments (Leg 2 and Leg 4) was seldom documented. Of the 47 patients with documented blood glucose levels, the overall occurrence rate of hyperglycemia was 13%. This is well below the 33-48% found in the civilian studies (See Table 2-7). No patients had repeated legs of hyperglycemia documented. One is left to wonder the amount of hyperglycemia that occurred but was undocumented.

Hypothermia was the secondary insult with the smallest documented occurrence rate of 8%. This is consistent with other studies that report occurrence rates of 5-26%. In this study, Leg 2, the AOR medical treatment facility, was the leg with the highest documented rate of occurrence. The average temperature in the cargo bay of a C-141 where patients are transported is 59°F (Bridges, 2003) and 55°F in the patient transport area onboard the C-17 (Bridges, personal communication, 2006). Based on this study,

CCAT teams are doing an effective job in keeping their patients warm since no documented episodes of hypothermia were recorded for either Leg 3 or Leg 5.

When secondary insults were assessed together, Leg 2, the period of time the patient is at the AOR medical treatment facility, had the highest percentage of patients with secondary insults. Leg 2 also had the greatest number of secondary insults and the greatest number of patients with two or more secondary insults. These Leg 2 findings need to be discussed in the context of missing data but support the recommendation to place medical assets as far forward as the tactical situation allows providing essential care in theater. This war has seen a paradigm shift in the treatment of TBI patients where early aggressive decompression with large craniectomies with subsequent watertight closures is the standard. These craniectomies are occurring in AOR combat support hospitals in Iraq (during Leg 2) to provide the patient some protection from the significant changes in ICP that can occur during the 18-hour flight from the Middle East to the United States (Bell et al., 2009). Only by providing this essential care far forward will health care providers be able to meet the “Golden Hour” of trauma, the first 60 minutes following trauma when the chances of survival are greatest if surgery or advanced trauma life support can be provided (Strawder, 2006).

Over half of the study patients had at least one leg with a documented secondary insult. No doubt these episodes are underreported due to missing data, the austere wartime environment, and critical nature of the patient care where saving life or limb takes precedence over documenting physiologic measures. The association between secondary insults and poor outcomes is well documented. Therefore, since prevention is the goal in keeping secondary insults minimized, the military will be well served to

utilize these study results to every possible advantage despite their limitations.

Hyperthermia should be anticipated early in the clinical course and efforts implemented to minimize it. Care providers should remain vigilant for signs of impending hypoxia and hypotension through all legs of the transport process. Awareness of the possibility and negative effects of hyperglycemia should be fore-front in an effort to manage blood glucose levels before they get to hyperglycemic levels. Finally, providers should be recognized for their efforts in preventing hypothermia and encouraged to pursue evidence-based care recommendations appropriate for the military transport environment to help keep patients normothermic.

5.4 Aim 2

Determine if the occurrence of secondary insults in isolated TBI CCATT patients is associated with extent of injury (ISS), etiology of TBI (blast vs. non-blast injury), type of aircraft used for transport (C-17 vs. C-141), and year of occurrence (from beginning of OIF/OEF to most recent available data).

5.4.1 Extent of Injury

Results of the logistic regression analysis support the Kendall's Tau correlation between ISS and hyperthermia. A positive association indicates that as the injury severity score increases, the likelihood of documented hyperthermia increases. This result is supported by previous studies that found that the incidence of hyperthermia is higher in more severely injured cases (Diringer, Reaven, Funk & Uman, 2004; Stocchetti et al., 2002). A lack of a statistically significant relationship between ISS and other secondary insults and even GCS and secondary insults could be a result of small sample size, missing data, or lack of documentation rather than a true null effect. Review of the

cases with the worst outcomes also supports the conclusions that those with the worst outcomes have higher ISS, lower GCS, and multiple secondary insults even though age, etiology of injury and year of injury are all quite varied.

5.4.2 Etiology of TBI

Traditionally, TBI has been classified as blunt or penetrating. With the increased number of blast injuries as a result of OIF/OEF, TBI as a result of explosive blasts is being recognized as a distinct etiology (Ling, Bandak, Armonda, Grant & Ecklund, 2009). Explosive blasts can result in primary blast, blunt, or penetrating brain injuries and can be the result of primary, secondary, or tertiary blast injuries. Therefore, even though the overall association between etiology of TBI and secondary insults was not statistically significant, further exploration into the various etiology combinations was pursued.

Of the 64 CCATT patients in this study, 55% were injured by blasts and 39% had closed head injuries (See Figure 5.1). A 5-year study from 2003 to 2008 of military traumatic brain and spinal column injury found a similar break down in etiology with explosive blast injuries constituting 56% of the sample and 34% being closed head injuries (Bell et al., 2009). A study of TBI casualties of all severity levels by Warden (2006) found blasts to be the overwhelming wounding etiology resulting in 88% closed head injuries. These breakdowns in injury etiologies are allowing researchers to begin to explore the differences and similarities between blast and non-blast injuries and closed and penetrating injuries caused by both mechanisms. What are not being captured, however, are the primary blast injuries. Being able to identify and explore primary blast injuries would allow further exploration into this new category of traumatic brain injury.

A statistically significant correlation was found between hyperglycemia and etiology of injury ($\tau=.32, p=.02$). When this correlation was explored, 5 (83%) of the documented cases of hyperglycemia were found in patients whose injuries were the result of penetrating blast injuries. The remaining case of documented hyperglycemia occurred in a patient whose injury was caused by a penetrating non-blast injury. Previous research studying hyperglycemia in brain injured patients has used various injury etiologies for their samples (See Table 2-7) but none has stratified their results by etiology. Stress induced catecholamine release following acute TBI can result in elevated blood glucose levels (Liu-DeRyke, 2009). In addition, blast-induced mechanical tissue injury can lead to activation of the neuroendocrine-immune system and contribute to secondary brain injury (Cernak & Hoble-Haeusslein, 2010). Hyperglycemia is often seen as a reflection of the severity of injury. This association was not found in this study possibly due to the small occurrence of hyperglycemia. No statistical association was found between the occurrence of hyperglycemia and ISS, GCS, or disposition. Five of the documented cases of hyperglycemia were reported during Leg 2 while at the AOR medical treatment facility. Hyperglycemia during the first 24 hours of admission has been identified as an independent risk factor for increased mortality irrespective of the severity of injury along with two glucose bands, <60 and ≥ 160 mg/dl (Liu-DeRyke, 2009). Therefore, early recognition of hyperglycemia with efforts to keep blood glucose levels below 160 mg/dl may help minimize secondary insults in TBI patients. The potential relationship between hyperglycemia and etiology should be interpreted with caution. Due to the small sample size, missing data, and possible confounding variables, further investigation is warranted.

5.4.3 Type of Aircraft

There was a significant correlation between year and the type of aircraft used for transporting CCATT patients from the AOR to LRMC over the 4 years of the data base ($\tau=.56, p<.001$) as well as year and the aircraft used for transporting CCATT patients from LRMC to CONUS over the same period ($\tau=.40, p=.01$). During this time period, the C-141 was used more commonly early on but as the C-141 was phased out of patient transport, the C-17 became the aircraft of choice for patient transport and was used exclusively for both legs in 2006. A few studies have examined the in-flight conditions of combat aircraft as they relate to the care of critically injured patients (Schmelz, Bridges, Duong & Ley, 2003; McNeill, 2007). Some of the differences found between types of aircraft include the thermal environment, noise, light, and vibration. Therefore, even though the C-17 is the most common aircraft used currently for the transport of wartime casualties, it is important to look at the effects of various aircraft environments to help assess whether different environments onboard different types of aircraft affect the outcomes of the patients being transported. This study did not have a large enough sample size with complete data and outcome measures to be able to assess the effects of the different aircraft environments on patient outcomes. Some variables were found, however, to have significant correlations with the type of aircraft used for transport of these CCATT patients.

A significant association was found between the type of aircraft used for transport of CCATT patients from the AOR to LRMC and documented occurrences of hypoxia ($\chi^2=5.02, p=.04$) with the higher rate of occurrence documented on the C-17. Upon closer assessment, all episodes of hypoxia were documented prior to the Leg 3 transport

for those transported by the C-141 and six of the nine patients with episodes of hypoxia were documented prior to Leg 3 transport for those transported by the C-17. Therefore it would be unrealistic to assume the differences in aircraft environments had an effect on this association and possible mediating variables could be explored. A significant association was not found between documented hypoxia and the type of aircraft used for transport of CCATT patients from LRMC to CONUS ($\chi^2=.87, p=.43$).

A statistically significant association was also found between the type of aircraft used for the AOR to LRMC transport and the documented occurrence of hypotension ($\chi^2=4.39, p=.048$). Eighty-two percent of the patients with documented hypotension were transported by C-141s for Leg 3. Upon further assessment, 9 of the 11 patients had documented hypotension prior to the AOR to LRMC transport. Therefore, as above, it would be unwise to assume the aircraft environment had an effect on this association and mediating variables such as time since injury, severity of injury, and etiology of injury could be explored.

Finally, a significant correlation was found between the aircraft used for Leg 3 and the documented occurrence of hyperglycemia ($\tau=.38, p=.01$) with all documented cases of hyperglycemia occurring on the C-17. Further investigation found five out of the six documented hyperglycemic patients experienced their hyperglycemia prior to the Leg 3 transport. Therefore, conclusions about the correlation between the aircraft used for Leg 3 and documented occurrences of hyperglycemia need to be made with extreme caution.

The lack of statistically significant differences between the types of aircraft used for CCATT transport on the occurrence of secondary insults supports the United States

Air Force's CCATT concept of utilizing opportune cargo aircraft. The implications of being able to use various types of cargo aircraft for patient transport goes beyond patient outcomes, which is paramount, as it also impacts the logistical movement of aircraft intratheater, intertheater, and intercontinentally. Not having to consider the type of cargo aircraft used for patient transport makes one small piece of the Air Force's logistical maneuvering a bit easier. Continued assessment of the impact of the on-board aircraft environment needs to continue as additional types of airframes become available for patient transport.

The small sample size, amount of missing data, and possibilities of mediating variables prohibit conclusions about the effect of the aircraft environment on the occurrence of secondary insults from being confidently made. Continued efforts should be made to assess the in-flight aircraft environments of the airframes being used for patient transport in an effort to maximize patient outcomes.

5.4.4 Year of Occurrence

In addition to the significant correlation between aircraft and year of injury, the correlation between year of injury and documented occurrence of hyperglycemia was also statistically significant ($\tau=.33, p=.02$). All documented occurrences of hyperglycemia occurred in the last two years of the database. Hyperglycemia only documented in the later two year of the database begs one to question whether there really was a difference in occurrence of hyperglycemia or a change in practice where assessing for hyperglycemia in the wartime theater became more common as the war progressed. The lack of documented occurrence of hyperglycemia early on and the earlier discussion about the lack of documented occurrence of hyperglycemia outside the

hospital environment leads to even further speculation about the undocumented amount of hyperglycemia.

The question remains, when is the best time to transport critically ill patients? The assumption is the sooner the better. To date, studies have not been able to answer this question. Being able to look at the occurrence of documented secondary insults over a 4 year time frame has given a glimpse into this issue. The median time from injury to arrival at LRMC has decreased from 2.5 days in 2004 to 1 day in 2006. Likewise, the median time from injury to arrival in CONUS has decreased from 8 days in 2003 to 3.5 days in 2006. Over the course of these changes, there has not been a significant change in the occurrence of secondary insults. Even though we would like to see a decline in secondary insults, based on this data, we can conclude that moving the patients sooner has not had an associated increase or decrease in the occurrence of documented secondary insults. More complete data with well defined disposition status is needed before associations can be made further between time in theater, duration of transport legs, and outcomes.

5.5 Strengths and Limitations

The WCCATD used for this study is the only one known of its kind. Therefore, this study is unique and important as it contributes to the state of the science on CCATT patients prior to their return to the United States. One of this study's strengths is the sample in that it includes the entire population of isolated TBI CCATT patients returning from Iraq and Afghanistan from October 2001 through May 2006. In addition, the 5 year time period allows assessment of variables over time. Being able to select out TBI

patients with only an isolated injury, even though they are a small percentage of TBI casualties, helps contribute to the understanding of TBI in military casualties.

Many of the limitations of this study have been included with the discussion of findings; the biggest being that of missing data. Additional limitations include those often found in secondary data analysis, which includes little or no control over what or how data were collected. To somewhat address this issue, many of this study's variables rely on highest and lowest physiologic measures. However, episodes of secondary insults may have occurred and not been recorded. Omission of physiologic measure documentation can be understood especially in the acute period of critically injured casualties at far forward operating locations and in austere environments. Information for complete legs of the transport process was also found to be missing. Complete legs of missing data could be a result of missing records especially early on in the war when medical record processes were being revised. The greatest amount of complete legs of missing data were found to be from CCATT flights suggesting difficulty in getting these legs of data incorporated into the patients' permanent medical record. Even if one were to assume the occurrence of secondary insults was similar for those patients with complete sets of missing leg data, the resulting occurrence of secondary insults found would still be within the range of secondary insult occurrence found in previous studies (see Table 5-1). This supports the conclusion that secondary insults are prevalent in the military CCATT population as well as the civilian TBI population. When the original database was created, multiple sources by multiple mechanisms were used which can lead to measurement error. Although numerous procedures were established by the primary researchers in ensuring the data were reliable and valid, many of these

limitations are inherent in secondary data analysis. Finally, even though the study included the entire population, the number of cases was small enough to allow only superficial analysis into subgroup variations.

5.6 Implications for Practice and Research

This study was undertaken in an attempt to determine where secondary insults of TBI CCATT patients were occurring before they returned to the United States. Since it is well documented that secondary insults lead to worse outcomes and the best treatment is prevention, it was hoped identifying which secondary insults occur and where they occur would lead to more informed and focused prevention. With the finding of increasing hyperthermia during the course of care from injury to the return to the United States, evidence based practice measures should be explored to reduce fever and infection. Measures to reduce fever and infection need to be explored in the context of the military battlefield and air medical transport environments. Military medical providers are providing the highest quality state-of-the-art care in the most austere environments from the battlefield to the casualty's return home days later. Providing insight to these medical providers on the occurrence of secondary insults of traumatic brain injured casualties hopefully will increase prevention thus optimizing outcomes.

This study supports Air Force policy. Currently CCATTs use opportune cargo aircraft to transport critically ill or injured patients. By not finding a significant difference between patients transported in the C-17 versus the C-141 aircraft, this Air Force policy is reinforced. The decision to transport patients earlier before they are stabilized is also supported by this study. Patients transported within one day of injury out of theater and within 3-4 days to the United States did not have any greater

occurrence of secondary insults than patients with delayed transport. Both of these findings have logistical implications for the Air Force and potential cost savings when the type of aircraft used (C-17 vs. C-141) and the timing in transport does not have a detrimental impact on the patient. Because of the limitations already discussed, further studies assessing aircraft environments and timing of transport would further support these assertions. Additionally, as other types of aircraft are more commonly used for patient transport, additional studies will need to be conducted to assure the safety and efficacy of their aircraft environment.

Even though this study begins to explore the relationships between secondary insults and TBI CCATT patients, additional studies with more complete data and detailed outcome measures are warranted. In an effort to provide more complete data, patient medical records should be standardized across services and begun if not at the point of injury, at the first medical treatment facility in the AOR. This standardized medical record should then follow the patient all the way through the transport system to definitive care facilities in the United States and become a permanent part of the patient's medical record. Additionally, outcome measures such as disposition, functional status, and GOS should be incorporated into the medical records to facilitate assessment of long term effects of injury and treatment.

Research of secondary insults of TBI should be expanded to include TBI in polytrauma CCATT patients. The population of polytrauma patients with TBI is much larger than isolated TBI patients. Taking what we have learned about isolated TBI CCATT patients and expanding it to the polytrauma patient will potentially lead to more

generalizable results as we continue to build the body of knowledge regarding TBI CCATT patients.

An attempt was made in this study to begin to look at patient differences based on etiology of blast and non-blast injuries resulting in closed and penetrating head injuries. Primary blast injuries is a recently identified etiology of TBI and one not parceled out in this or most other studies. Since little is known about the effects of primary blast injuries especially in TBI patients, studies should be conducted targeting this injury etiology.

Even though this study addressed the entire population of isolated TBI CCATT patients returning from Iraq and Afghanistan, it is hoped some of these same ideas can be explored for application with civilian TBI patients encountering extended transport or in austere environments.

APPENDIX A - Tables

Table A-1 Variable Values and Origins

Variable	Label	Value	Location from WCCATD	Notes
ID	Subject Number	Numeric	Subjcorr	
Gender	Gender	0 – male 1 – female	Gender	
Age	Age	Numeric	Age	Verified with Birthday and DateofEvent
Service	Service Branch Code	1 – Army 2 – Marine Corps 3 – Air Force 4 – Navy 5 – Foreign National 6 – US State Department	Serv_bra	
DateofInj	Date of Injury	Date	DateofEvent; JTTRDateWounded	
Blast	Type of Injury	1 – Penetrating 2 – Blunt 3 – Blast 4 – Heat Stroke	Coded from the following variables: explosion; gsw; fragment; mvc; fall; exposure; drown; blunt	Verified with CauseofInjury and InjuryRemarks narrative variables
Isolated	Isolated Head Injury	0 – Yes 1 – No	InjuryGroup	
JTTRISS05	Injury Severity Score	Numeric	JTTRISS05	
GCSFR	Initial GCS	Numeric	HospAdmGCS JTTRLOCGCSTotal1	Verified with narrative variables
GCSM	Initial GCS Motor	Numeric	HosptAdmMotor JTTRLOCMotorScore1	Verified with narrative

				variables
L1LGCS	Lowest recorded GCS during Leg 1	Numeric	JTTRLOCGCSTotal1 JTTRLOCGCSTotal2 JTTRLOCGCSTotal3 JTTRLOCGCSTotal4 JTTRLOCGCSTotal5	
L1LSBP	Lowest recorded SBP during Leg 1	Numeric	JTTRLOCSBP1 JTTRLOCSBP2 JTTRLOCSBP3 JTTRLOCSBP4 JTTRLOCSBP5	
L1LSpO2	Lowest recorded SpO2 during Leg 1	Numeric	ccatt_co HISTORYR HistoryofPresentIllness InjuryCharacteristicsNotes HospOtherNotes JTTRCasualtyComments JTTRLOCDataNotes HTTRLOCNotes	Extracted from narrative notes
L1HTemp	Highest recorded temperature in C during Leg 1	Numeric to 1 decimal	JTTRLOCTempC1 JTTRLOCTempF1 JTTRLOCTempC2 JTTRLOCTempF2 JTTRLOCTempC3 JTTRLOCTempF3 JTTRLOCTempC4 JTTRLOCTempF4 JTTRLOCTempC5 JTTRLOCTempF5	Fahrenheit converted to Celsius
L1LTemp	Lowest recorded temperature in C during Leg 1	Numeric to 1 decimal	JTTRLOCTempC1 JTTRLOCTempF1 JTTRLOCTempC2 JTTRLOCTempF2 JTTRLOCTempC3 JTTRLOCTempF3 JTTRLOCTempC4 JTTRLOCTempF4 JTTRLOCTempC5 JTTRLOCTempF5	Fahrenheit converted to Celsius
L1HGluc	Highest recorded blood glucose level during Leg 1	Numeric	ccatt_co HISTORYR HistoryofPresentIllness InjuryCharacteristicsNotes HospOtherNotes JTTRCasualtyComments JTTRLOCDataNotes	Extracted from narrative notes

			HTTRLOCNotes	
L1ICP	Highest recorded ICP during Leg 1	Numeric	ccatt_co HISTORYR HistoryofPresentIllness InjuryCharacteristicsNotes HospOtherNotes JTTRCasualtyComments JTTRLOCDataNotes HTTRLOCNotes	Extracted from narrative notes
L1CPP	Lowest recorded CPP during Leg 1	Numeric	ccatt_co HISTORYR HistoryofPresentIllness InjuryCharacteristicsNotes HospOtherNotes JTTRCasualtyComments JTTRLOCDataNotes HTTRLOCNotes	Extracted from narrative notes
L2Arrived	Date arrived at AOR MTF	Date	destname HospDateAdmission HospPtDisposition HospDateDisposition	Variables used to determine hospital (Leg) and associated admission date
L2LGCS	Lowest recorded GCS for Leg 2	Numeric	HospAPACHEIIGCS1 SecGCSTotal1 SecGCSTotal2 SecGCSTotal3 HospAdmGCS if AOR MTF	APACHEII – 24 hours before flight to LRMC Sec...1 – Admission to AOR MTF Sec...2 – Post resuscitation Sec...3 – First 24 hrs
L2LSBP	Lowest recorded SBP for Leg 2	Numeric	SecSBP1 SecSBP2 SecSBP3 HospAdmSBP if AOR MTF	
L2LSpO2	Lowest	Numeric	SecSpO21	

	recorded SpO2 for Leg 2		SecSpO22 SecSpO23 HospAdmSpO2 if AOR MTF	
L2HTemp	Highest recorded temperature for Leg 2	Numeric to 1 decimal	HospAPACHETemp1 APACHE2Temp SecTemp1high SecTemp2high SecTemp3high HospAdmTemp if AOR MTF	
L2LTemp	Lowest recorded temperature for Leg 2	Numeric to 1 decimal	HospAPACHETemp1 APACHE2Temp SecTemp1low SecTemp2low SecTemp3low HospAdmTemp if AOR MTF	
L2HGluc	Highest recorded blood glucose for Leg 2	Numeric	SecGluc1high SecGluc2high SecGluc3high HospAdmGluc if AOR MTF	
L2ICP	Highest recorded ICP for Leg 2	Numeric	SecICP1 SecICP2 SecICP3 HospAdmICP if AOR MTF	
L2CPP	Lowest recorded CPP for Leg 2	Numeric	SecCPP1 SecCPP2 SecCPP3 HospAdmCPP if AOR MTF	
L3CCATTStart	Date CCATT assumed care from AOR MTF	Date	CCATTTransportRoute DateCCATT	Variables used to determine CCATT route (Leg) and associated start date for this and following L3 variables.
L3Airframe	CCATT	1 – C-130	CCATTAirframeType	

	Aircraft	2 – C-141 3 – C-17		
L3Flighttime	Total mission time in minutes for Leg 3	Numeric	totimem	
L3LGCS	Lowest recorded GCS for Leg 3	Numeric	CCATTPreCCATTGCS CCATTPostCCATTGCS SecGCSTotal6	Sec...6 – CCATT AOR to LRMC
L3LSBP	Lowest recorded SBP for Leg 3	Numeric	CCATTPreflightSBP CCATTPostFlightSBP SecSBP6 FSSBP1 – FSSBP20	
L3LSpO2	Lowest recorded SpO2 for Leg 3	Numeric	CCATTPreSpO2 CCATTPostSpO2 SecSpO26 FSSpO21 – FSSpO220	
L3HTemp	Highest recorded temperature for Leg 3	Numeric to 1 decimal	CCATTPreflightTemp CCATTPostFlightTemp SecTemp6high FSTemp1 – FSTemp20	
L3LTemp	Lowest recorded temperature for Leg 3	Numeric to 1 decimal	CCATTPreflightTemp CCATTPostFlightTemp SecTemp6low FSTemp1 – FSTemp20	
L3HGluc	Highest recorded blood glucose for Leg 3	Numeric	SecGluc6high FSGluc1 – FSGluc11	
L3ICP	Highest recorded ICP for Leg 3	Numeric	SecICP6 FSICP1 – FSICP20	
L3CPP	Lowest recorded CPP for Leg 3	Numeric	SecCPP6 FSCPP1 – FSCPP20	
L4Arrived	Date arrived at LRMC	Date	destname HospDateAdmission HospPtDisposition HospDateDisposition	Variables used to determine hospital (Leg) and associated admission date

L4LGCS	Lowest recorded GCS for Leg 4	Numeric	HospAdmGCS if LRMC	
L4LSBP	Lowest recorded SBP for Leg 4	Numeric	HospAdmSBP if LRMC	
L4LSpO2	Lowest recorded SpO2 for Leg 4	Numeric	HospAdmSpO2 if LRMC	
L4HTemp	Highest recorded temperature for Leg 4	Numeric to 1 decimal	APACHE3temp APACHE4temp HospAdmTemp if LRMC	APACHE3 – first 24 hrs at LRMC APACHE4 – last 24hrs at LRMC
L4LTemp	Lowest recorded temperature for Leg 4	Numeric to 1 decimal	APACHE3temp APACHE4temp HospAdmTemp if LRMC	
L4HGluc	Highest recorded blood glucose for Leg 4	Numeric	HospAdmGluc if LRMC	
L4ICP	Highest recorded ICP for Leg 4	Numeric	HospAdmICP if LRMC	
L4CPP	Lowest recorded CPP for Leg 4	Numeric	HospAdmCPP if LRMC	
L5CCATTStart	Date CCATT assumed care from AOR MTF	Date	CCATTTransportRoute DateCCATT	Variables used to determine CCATT route (Leg) and associated start date for this and following L3

				variables.
L5Airframe	CCATT Aircraft	1 – C-130 2 – C-141 3 – C-17	CCATT AircraftType	
L5Flighttime	Total mission time in minutes for Leg 5	Numeric	totimem	
L5LGCS	Lowest recorded GCS for Leg 5	Numeric	CCATTPreCCATTGCS CCATTPostCCATTGCS SecGCSTotal7	Sec...7 – CCATT LRMC to CONUS
L5SBP	Lowest recorded SBP for Leg 5	Numeric	CCATTPreflightSBP CCATTPostFlightSBP SecSBP7 FSSBP1 – FSSBP20	
L5LSpO2	Lowest recorded SpO2 for Leg 5	Numeric	CCATTPreSpO2 CCATTPostSpO2 SecSpO27 FSSpO21 – FSSpO220	
L5HTemp	Highest recorded temperature for Leg 5	Numeric to 1 decimal	CCATTPreflightTemp CCATTPostFlightTemp SecTemp7high FSTemp1 – FSTemp20	
L5LTemp	Lowest recorded temperature for Leg 5	Numeric to 1 decimal	CCATTPreflightTemp CCATTPostFlightTemp SecTemp7low FSTemp1 – FSTemp20	
L5HGluc	Highest recorded blood glucose for Leg 5	Numeric	SecGluc7high FSGluc1 – FSGluc11	
L5ICP	Highest recorded ICP for Leg 5	Numeric	SecICP7 FSICP1 – FSICP20	
L5CPP	Lowest recorded CPP for Leg 5	Numeric	SecCPP7 FSCPP1 – FSCPP20	
L6Arrived	Date arrived in CONUS	Date	destname HospDateAdmission	Variables used to determine hospital (Leg) and associated

				admission date
LOC	Loss of consciousness	0 – NO 1 – time unknown 2 - <1 hour 3 – 1-24 hours 4 - >24 hours	LOC	
Disposition	Last known patient disposition	1 – Transfer from ICU to Medical-surgical unit 2 – Discharge from medical facility – return to duty 3 – Discharge from medical facility – convalescent leave 4 – Transport CONUS by CCATT 5 – Transport to CONUS by routine AE 6 – Transport to another facility in CONUS 7 – Died in ICU	HospPtDisposition HospitalFinalDisposition	

		8 – Died after transfer from ICU 9 – Disposition not available 10 – Transport to LRMC by CCATT 11 – Still in ICU at Day 7 12 – Transport AOR to LRMC not by CCATT 13 – Civilian transport 14 – Transport by other nation CCATT 15 – Transport by MEDEVA C to AOR MTF 16 – Still on Med-Surg Unit on Day 7		
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Table A-2 New Variable Values and Origins

New Variable	Label	Value	Location from Study Database	Notes
YearofInj	Year of Injury	0 - 2003 1 - 2004 2 - 2005	DateofInj	Transcription confirmed with 100%

		3 - 2006		verification
BIXCP	Blast/NonBlast Injury by Closed/ Penetrating	0 – NonBlast Closed 1 – NonBlast Penetrating 2 – Blast Closed 3 – Blast Penetrating	Blast	Verified with CauseofInjury and InjuryRemarks narrative variables in WCCATD
BlvsNBI	Blast vs NonBlast	0 – Blast 1 – NonBlast	Blast	Blast Values: 3 - 0 1,2,4 - 1
ISSC	Injury Severity Score Coded	0 – Minor 1 – Moderate 2 – Mod/Severe 3 – Sev/Critical	JTTRISS05	Minor: 1-9 Moderate: 10-15 Mod/Sev: 16-24 Sev/Crit: ≥25
GCSC	Initial GCS Coded	0 – Mild 1 – Moderate 2 – Severe	GCSFR	Mild: 14-15 Moderate: 9-13 Severe: 3-8
L1LSBPC	Leg 1 Low SBP Coded	0 – No 1 – Yes	L1LSBP	
L1LSpO2C	Leg 1 Low SpO2 Coded	0 – No 1 – Yes	L1LSpO2	
L1HTempC	Leg 1 High Temp Coded	0 – No 1 – Yes	L1HTemp	
L1LTempC	Leg 1 Low Temp Coded	0 – No 1 – Yes	L1LTemp	
L1HGlucC	Leg 1 High Glucose Coded	0 – No 1 – Yes	L1HGluc	
L1ICPC	Leg 1 High ICP Coded	0 – No 1 – Yes	L1ICP	
L1CPPC	Leg 1 Low CPP Coded	0 – No 1 - Yes	L1CPP	
L2LSBPC	Leg 2 Low SBP Coded	0 – No 1 – Yes	L2LSBP	
L2LSpO2C	Leg 2 Low SpO2 Coded	0 – No 1 – Yes	L2LSpO2	
L2HTempC	Leg 2 High Temp Coded	0 – No 1 – Yes	L2HTemp	
L2LTempC	Leg 2 Low Temp Coded	0 – No 1 – Yes	L2LTemp	
L2HGlucC	Leg 2 High Glucose Coded	0 – No 1 – Yes	L2HGluc	
L2ICPC	Leg 2 High ICP Coded	0 – No 1 – Yes	L2ICP	

L2CPPC	Leg 2 Low CPP Coded	0 – No 1 – Yes	L2CPP	
L3PlaneRC	Leg 3 CCATT Aircraft Recoded	0 – C-141 1 – C-17	L3Airframe	L3Airframe values: 1 – missing 2 – 0 3 – 1
L3LSBPC	Leg 3 Low SBP Coded	0 – No 1 – Yes	L3LSBP	
L3LSpO2C	Leg 3 Low SpO2 Coded	0 – No 1 – Yes	L3LSpO2	
L3HTempC	Leg 3 High Temp Coded	0 – No 1 – Yes	L3HTemp	
L3LTempC	Leg 3 Low Temp Coded	0 – No 1 – Yes	L3LTemp	
L3HGlucC	Leg 3 High Glucose Coded	0 – No 1 – Yes	L3HGluc	
L3ICPC	Leg 3 High ICP Coded	0 – No 1 – Yes	L3ICP	
L3CPPC	Leg 3 Low CPP Coded	0 – No 1 – Yes	L3CPP	
DItL4A	Days from Injury to L4 Arrival	Continuous	DateofInj L4Arrived	L4Arrived minus DateofInj
L4LSBPC	Leg 4 Low SBP Coded	0 – No 1 – Yes	L4LSBP	
L4LSpO2C	Leg 4 Low SpO2 Coded	0 – No 1 – Yes	L4LSpO2	
L4HTempC	Leg 4 High Temp Coded	0 – No 1 – Yes	L4HTemp	
L4LTempC	Leg 4 Low Temp Coded	0 – No 1 – Yes	L4LTemp	
L4HGlucC	Leg 4 High Glucose Coded	0 – No 1 – Yes	L4HGluc	
L4ICPC	Leg 4 High ICP Coded	0 – No 1 – Yes	L4ICP	
L4CPPC	Leg 4 Low CPP Coded	0 – No 1 – Yes	L4CPP	
L5LSBPC	Leg 5 Low SBP Coded	0 – No 1 – Yes	L5LSBP	
L5LSpO2C	Leg 5 Low SpO2 Coded	0 – No 1 – Yes	L5LSpO2	
L5HTempC	Leg 5 High Temp Coded	0 – No 1 – Yes	L5HTemp	
L5LTempC	Leg 5 Low	0 – No	L5LTemp	

	Temp Coded	1 – Yes		
L5HGlucC	Leg 5 High Glucose Coded	0 – No 1 – Yes	L5HGluc	
L5ICPC	Leg 5 High ICP Coded	0 – No 1 – Yes	L5ICP	
L5CPPC	Leg 5 Low CPP Coded	0 – No 1 – Yes	L5CPP	
DItL6A	Days from Injury to CONUS Arrival	Continuous	DateofInj L6Arrived	L6Arrived minus DateofInj
Dispo3Cats	Disposition in 3 Categories	0 – D/C, Con Leave, Out Pt Tx 1 – Transfer to Inpt Facility 2 – Died	Disposition	Disposition values: 0 – 2,3 1 – 6 2 – 7,8 Missing – 1,4,5,9,10,11,12, 13,14,15,16
LSBPT	Legs of LSBP	Continuous	L1LSBPC L2LSBPC L3LSBPC L4LSBPC L5LSBPC	Add leg variables
LSBPYN	Occurrence of LSBP	0 – No 1 – Yes	LSBPT	If greater than 0 then 1
LSpO2T	Legs of LSpO2	Continuous	L1LSBPC L2LSBPC L3LSBPC L4LSBPC L5LSBPC	Add leg variables
LSpO2YN	Occurrence of LSpO2 Yes or No	0 – No 1 – Yes	LSpO2T	If greater than 0 then 1
HTempT	Legs of HTemp	Continuous	L1HTempC L2HTempC L3HTempC L4HTempC L5HTempC	Add leg variables
HTempYN	Occurrence of HTemp Yes or No	0 – No 1 – Yes	HTempT	If greater than 0 then 1
LTempT	Legs of LTemp	Continuous	L1LTempC L2LTempC L3LTempC	Add leg variables

			L4LTempC L5LTempC	
LTempYN	Occurrence of LTemp Yes or No	0 – No 1 – Yes	LTempT	If greater than 0 then 1
HGlucT	Legs of HGluc	Continuous	L1HGlucC L2HGlucC L3HGlucC L4HGlucC L5HGlucC	Add leg variables
HGlucYN	Occurrence of HGluc Yes or No	0 – No 1 – Yes	HGlucT	If greater than 0 then 1
TICP	Legs of High ICP	Continuous	L1ICPC L2ICPC L3ICPC L4ICPC L5ICPC	Add leg variables
TCPP	Legs of Low CCP	Continuous	L1CPPC L2CPPC L3CPPC L4CPPC L5CPPC	Add leg variables
TICPYN	Occurrence of High ICP Yes or No	0 – No 1 – Yes	TICP	If greater than 0 then 1
TCPPYN	Occurrence of Low CPP Yes or No	0 – No 1 – Yes	TCPP	If greater than 0 then 1
HTLSpo2	High Temp LSpO2 Combination	0 – No 1 – Yes	HTempYN LSpO2YN	If both 1 then 1
HTLSBP	High Temp LSBP Combination	0 – No 1 – Yes	HTempYN LSBPYN	If both 1 then 1
SIT	Legs of Secondary Insults	Continuous	LSBPT LSpO2T HTempT LTempT HGlucT	Add secondary insult variables
L1SIT	Leg 1 Secondary Insult Total	Continuous	L1LSBPC L1LSpO2C L1HTempC L1LTempC L1HGlucC	Add leg secondary insult variables

L2SIT	Leg 2 Secondary Insult Total	Continuous	L2LSBPC L2LSpO2C L2HTempC L2LTempC L2HGlucC	Add leg secondary insult variables
L3SIT	Leg 3 Secondary Insult Total	Continuous	L3LSBPC L3LSpO2C L3HTempC L3LTempC L3HGlucC	Add leg secondary insult variables
L4SIT	Leg 4 Secondary Insult Total	Continuous	L4LSBPC L4LSpO2C L4HTempC L4LTempC L4HGlucC	Add leg secondary insult variables
L5SIT	Leg 5 Secondary Insult Total	Continuous	L5LSBPC L5LSpO2C L5HTempC L5LTempC L5HGlucC	Add leg secondary insult variables

Table A-3 Skewness and Kurtosis of Continuous Variables

	Age	ISS	Days to LRMC	Days to CONUS
N	64	59	56	43
Skewness	1.58	0.03	2.53	1.81
Std. Error of Skewness	0.30	0.31	0.32	0.36
Z-score of Skewness	5.3	0.1	7.9	5.0
Kurtosis	2.90	-0.74	6.34	3.84
Std. Error of Kurtosis	0.59	0.61	0.63	0.71
Z-score of Kurtosis	4.9	-1.2	10.1	5.4

Table A-4 Correlation Matrix of Study Variables

Kendall's Tau		ISS	Blast	Year	Aircraft L3	Aircraft L5
ISS	Correlation	1.00				
	Sig.					
	N	59				
Blast	Correlation	-.100	1.00			
	Sig.	.366				
	N	59	64			
Year	Correlation	.036	.079	1.00		
	Sig.	.731	.501			
	N	59	64	64		
Aircraft L3	Correlation	-.063	.026	.563**	1.00	
	Sig.	.579	.842	.000		
	N	56	61	61	61	
Aircraft L5	Correlation	.041	.089	.400*	.342*	1.00
	Sig.	.773	.598	.013	.040	
	N	36	36	36	36	36

* Significant at the 0.05 level (2-tailed)

** Significant at the 0.01 level (2-tailed)

Table A-5 Collinearity Statistics

Independent Variables	Tolerance	VIF
Injury Severity Score	.966	1.035
Blast vs. Non-Blast	.980	1.021
Year of Injury	.566	1.768
AOR to LRMCAircraft	.608	1.645
LRMCAircraft to CONUS Aircraft	.790	1.266

Table A-6 Logistic Regression Predicting Likelihood of Documented Hypotension (n=55)

Variable	B	S.E.	Wald	df	p	Odds Ratio	95%CI Lower	95% CI Upper
ISS	.06	.05	1.48	1	.22	1.06	.96	1.17
Blast vs. Non-Blast	.83	.84	.99	1	.32	2.30	.44	11.95
Year of Injury	.78	.74	1.11	1	.29	2.18	.51	9.29
Aircraft for Leg 3	-2.07	1.14	3.32	1	.07	.13	.01	1.17
Constant	-3.74	1.74	4.64	1	.03	.02		

Table A-7 Logistic Regression Predicting Likelihood of Documented Hypoxia (n=45)

Variable	B	S.E.	Wald	df	p	Odds Ratio	95%CI Lower	95% CI Upper
ISS	.03	.05	.25	1	.62	1.03	.93	1.13
Blast vs. Non-Blast	-.08	.74	.01	1	.91	.92	.22	3.94
Year of Injury	.06	.58	.01	1	.92	1.06	.34	3.30
Aircraft for Leg 3	1.50	.91	2.76	1	.10	4.50	.76	26.56
Constant	-2.50	1.52	2.68	1	.10	.08		

Table A-8 Logistic Regression Predicting Likelihood of Documented Hypothermia (n=53)

Variable	B	S.E.	Wald	df	p	Odds Ratio	95%CI Lower	95% CI Upper
ISS	.04	.06	.36	1	.55	1.04	.92	1.18
Blast vs. Non-Blast	-.70	1.00	.48	1	.49	.50	.07	3.57
Year of Injury	.272	.88	.10	1	.76	1.31	.24	7.30
Aircraft for Leg 3	-.53	1.25	.18	1	.67	.59	.05	6.83
Constant	-2.89	1.98	2.14	1	.14	.06		

APPENDIX B – Institutional Review Board Approval



University of Maryland, Baltimore
 Institutional Review Board (IRB)
 Phone: (410) 706-5037
 Fax: (410) 706-4189
 Email: hrpo@som.umaryland.edu

New Study Approval Notification

Date: March 22, 2010

To: Mary Johantgen
 From: IRB Chair/Vice Chair: Christopher deFilippi
 RE: HP-00044567
 Risk designation: Minimal Risk
 Submission Date: 2/15/2010
 Original Version #: N/A

Approval for this project is valid from 3/22/2010 to 3/21/2011

This is to certify that the University of Maryland, Baltimore (UMB) Institutional Review Board (IRB) has fully approved the above referenced protocol entitled, "*Secondary Insults of Traumatic Brain Injury in CCATT Patients Returning from Iraq/Afghanistan*".

The IRB has determined that this protocol qualifies for expedited review pursuant to Federal regulations 45 CFR 46.110, 21 CFR 56.110, & 38 CFR 16.110 category(ies).

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

Please be aware that only valid IRB-approved informed consent forms may be used when written informed consent is required.

Investigators are reminded that the IRB must be notified of any changes in the study. In addition, the PI is responsible for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject (45 CFR 46.103(4)(iii)).

DHHS regulations at 45 CFR 46.109 (e) require that **continuing review** of research be conducted by the IRB at intervals appropriate to the degree of risk and **not less than once per year**. The regulations make **no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval**. You will receive continuing review email reminder notices prior to study expiration; however, it is your responsibility to submit your continuing review report in a timely manner to allow

adequate time for substantive and meaningful IRB review and assure that this study is not conducted beyond the expiration date. Investigators should submit continuing review reports in the electronic system at least six weeks prior to the IRB expiration date.

In addition, you must inform the IRB of any new and significant information that may impact a research participants' safety or willingness to continue in your study and any unanticipated problems involving risks to participants or others.

Research activity involving veterans or the Baltimore VA Maryland Healthcare System (BVAMHCS) as a site, must also be approved by the BVAMHCS Research and Development Committee prior to initiation. Contact the VA Research Office at 410-605-7131 for assistance.

The UMB IRB is organized and operated according to guidelines of the International Council on Harmonization, the United States Office for Human Research Protections and the United States Code of Federal Regulations and operates under Federal Wide Assurance No. FWA00007145.

APPENDIX C – Data Use Agreement

20 Jan 2010

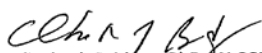
FROM: Elizabeth Bridges, PhD RN
1959 NE Pacific T608C
University of Washington School of Nursing
Seattle WA 98103

TO: Susan Dukes, Maj, USAF, NC
655 West Lombard Street
Baltimore, MD 21201

SUBJECT: Data Sharing Request

Sue

It is my pleasure to provide to you the requested data from my research study: Wartime Critical Care Air Transport. As we have discussed I will provide first the data specific to the isolated head injury patients. I will forward these data to you upon receipt of your IRB approval. Best of luck with your research



Elizabeth Bridges, PhD, AN CCNS, FCCM, FAAN
Principal Investigator

14 Dec 09

MEMORANDUM FOR COL ELIZABETH BRIDGES

FROM: Susan Dukes, Maj, USAF, NC
 655 West Lombard Street
 Baltimore, MD 21201

SUBJECT: Data Sharing Request

1. This letter is to official request use of portions of the Wartime Critical Care Air Transport Database. I am a full-time Air Force Institute of Technology sponsored PhD student in Nursing Science at the University of Maryland, Baltimore. My research interest is the critical care air transport of traumatic brain injured patients. I have successfully completed all required course work, preliminary and comprehensive exams, and have successfully defended my research proposal. As an active duty Air Force nurse officer, I am working to meet the tight timelines set by the Air Force. My dissertation needs to be completed and defended by July 2010. Therefore, I am extremely grateful for your willingness to share data for my research project.

2. The title of my study is "Secondary Insults of Traumatic Brain Injury in CCATT patients returning from Iraq/Afghanistan." The specific aims include:

1. Describe the occurrence of secondary insults in TBI patients transported by CCATTs.
2. Determine if the occurrence of secondary insults in TBI CCATT patients is associated with:
 - a. extent of injury (isolated TBI vs. TBI with polytrauma)
 - b. etiology of TBI (blast vs. non-blast injury)
 - c. year of occurrence (from beginning of OIF/OEF to most recent available data)

The availability of the data is desired by 25 Jan 10. Attached is a list of the data elements desired.

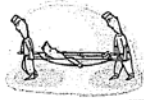



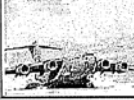

3. Deidentified data is desired to minimize the risk to loss of confidentiality. Therefore, please do not include the following: cite numbers, birthdates, social security numbers, Joint Theater Trauma Registry (JTTR) Codes, and locations of area of responsibility (AOR) hospitals. Unique patient identifies not linked to any other identifying information are needed to identify multiple rows of data for the same patient within the database. Through these means, the data will be of most benefit for my research but will provide confidentiality to the patients within the database. The research proposal for this project will meet the Investigational Review Board (IRB) of the University of Maryland.

4. These data will be used for the express purpose of answering research questions and will not be used for any other purpose. When disseminating the results of this research in publications, I will be the primary author with yourself and Dr. Meg Johantgen as additional authors.

SUSAN F. DUKES, Major, USAF, NC
 PhD AFIT Student
 University of Maryland, Baltimore

Attachment:
 Data Elements Requested

Attachment: Data Elements Requested

					
Leg 1: Point of Injury to	Leg 2: AOR MTF	Leg 3: CCATT AOR to	Leg 4: LRMC, Germany	Leg 5: CCATT LRMC to	CONUS
Gender	Lowest SBP	Date/Time CCATT Assumed Care	Lowest SBP	Date/Time CCATT Assumed Care	Date/Time CCATT Relinquished Care
Age	Lowest SpO ₂	Length of Flight	Lowest SpO ₂	Length of Flight	
Service	Highest Temperature	Lowest SBP	Highest Temperature	Lowest SBP	
Date/Time of Injury	Lowest Temperature	Lowest Sp O ₂	Lowest Temperature	Lowest SpO ₂	
Etiology of TBI: non-blast vs. blast	Highest Glucose	Highest Temperature	Highest Glucose	Highest Temperature	
Extent of Injury: Isolated TBI vs. TBI & polytrauma	Highest ICP	Lowest Temperature	Highest ICP	Lowest Temperature	
Lowest GCS	Date/Time Arrived	Highest Glucose	Date/Time Arrived	Highest Glucose	
Lowest SBP		Highest ICP		Highest ICP	
Lowest SpO ₂					
Highest Temperature					
Lowest Temperature					
Highest Glucose					
Highest ICP					

AOR - Area of Responsibility
 MTF - Medical Treatment Facility
 CCATT – Critical Care Air Transport Team
 LRMC – Landstuhl Regional Medical Center
 CONUS – Continental United States
 TBI – Traumatic Brain Injury
 SBP – Systolic Blood Pressure
 SpO₂- Oxygen Saturation
 GCS – Glasgow Coma Scale
 ICP – Intracranial Pressure

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