Exploring canine trauma and hemorrhage as a translational model: Epidemiology, shock index and tissue oxygen levels

A Thesis SUBMITTED TO THE FACULTY OF UNIVERSITY OF MINNESOTA

BY

Kelly Elizabeth Wilke

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTERS OF SCIENCE

Advisor: Gregory Beilman, MD

December 2012

Acknowledgements

I would like to thank Dr. Russell Luepker for "taking a chance" on admission of a clinical veterinarian to the Masters in Clinical Research program. I feel that I've achieved my goals of creating collaborative and translational opportunities with the world of human medicine.

I extend particular thanks to Dr. Greg Beilman, my primary advisor, for his ongoing mentorship and patience with me. You are an amazing role model, and your advice has not only helped provide me with career direction, but also helped me appreciate my role as a clinical faculty member at the University of Minnesota.

Above all, I am eternally grateful to my family for their continued support while I pursue my passion for advancing clinical veterinary medicine, teaching and research. I constantly strive to be the individual I expect my children to be (Ethan, Allison and Chase), but in reality, I continue to depend on their unconditional love and support when "mom is at work" for extended periods of time. Thank you for all of the smiles and hugs when I finally return home. Most importantly, I am eternally grateful to my husband, Andrew, for being a continued rock of support "for better and for worse, and in times of sickness and in health".

Table of Contents

List of Tables

List of Figures

INTRODUCTION:

This body of work represents initial efforts to justify the use of naturally occurring trauma in dogs as a translational model for improving trauma patient care in dogs and humans, alike (Figure 1, below). The idea for developing canine trauma as a translational model is a direct result of opportunities realized during participation in the Masters of Clinical Research program. The concept of evaluating naturally occurring diseases in dogs to enhance human patient care has become more prevalent in recent years, particularly in the fields of oncology[1], epilepsy[2] and gene therapy.[3] A canine trauma model offers an opportunity to leverage information learned from experimental canine trauma models in concert with information from spontaneous ("natural") canine models that occur in the clinical setting. The first manuscript represents a review of the veterinary and human trauma literature, drawing similarities between injury patterns in both populations and proposing the utilization of naturally occurring trauma in dogs as a model for human trauma ("**Naturally occurring canine trauma: A model for early and late causes of human trauma morbidity and mortality**"). Drs. Claire Sharp and Cynthia Adams contributed to the literature review and summary of articles included in the paper; generation of the manuscript involved all listed authors under the guidance and mentorship of Dr. Greg Beilman.

The second manuscript ("**A multi-center eight-week prospective cohort study of 315 dogs sustaining trauma"**) represents the initial efforts of the multicenter, multidisciplinary Spontaneous Trauma in Animals Team (STAT). The manuscript will be

submitted to the Journal of the Veterinary Medical Association (JAVMA). This group first formally met in January 2011 and established a primary goal to successfully plan, obtain funding for, and perform a multi-center prospective cohort study in anticipation of performing multi-center prospective clinical trials. The STAT infrastructure is designed in anticipation of performing future intervention studies. Study execution, expertise and resources are provided by the site investigator working group [Drs. Hall (UMN), Holowaychuk (OVC), Sharp (Tufts) and Reineke (UPenn)], Data Monitoring Committee [UMN: Drs. Byrnes (MD trauma surgeon), Beilman (MD trauma surgeon), Spector (pediatric epidemiologist), Leduc (biostatistician); UPenn: Dr. Otto (veterinary criticalists, translational researcher)] and Clinical Investigation Center [UMN: Kathy Stuebner (research coordinator)], respectively. Given the successful collaborative efforts of this first research project, the group is working toward obtaining funding for pre-Phase I and Phase II trials utilizing this spontaneous model in order to efficiently evaluate therapeutic interventions (e.g., novel fluid therapies, early goal directed therapy, mesenchymal stem cell therapy) and/or non-invasive monitoring techniques to guide therapy and improve outcome (e.g., near-infrared spectroscopy, biomarkers). The group has recently expanded to add 2 additional research sites (The Ohio State University and Michigan State University) and is currently enrolling patients in a similarly designed study evaluating scoring systems and outcome in feline trauma. It is a privilege to function as the founder and lead facilitator of this collaborative working group.

The third and fourth manuscripts evaluate the application of two triage tools adapted from human emergency and critical care medicine in canine patients. "**Tissue oxygen saturation (StO_2) in dogs presenting for acute hemorrhage**" assesses the InSpectra™ Tissue Spectrometer[a] in a population of acutely hemorrhaging dogs and "**Assessment of shock index in healthy dogs and dogs in hemorrhagic shock**" evaluates the utility of shock index (heart rate/systolic blood pressure) in the same population. The first project was internally funded by College of Veterinary Medicine's Small Companion Animal Grant, and co-lead by Drs. Sarah Gray and Kelly Hall (grant writing, case and data tracking, manuscript preparation). Dr. Sarah Gray presented the data at the International Veterinary Emergency and Critical Care Society conference in 2011 as part of her Emergency/Critical Care residency requirements. Drs. Schildt and Powell participated in classification of patient's shock level and manuscript creation. Dr. Ann Brearley (Biostatistical Design and Analysis Center, UMN) performed the biostatistical analysis and contributed to manuscript creation. The manuscript will be submitted to the Journal of Veterinary Emergency and Critical Care. Dr. Katie Peterson presented the shock index data in abstract form at the International Veterinary Emergency and Critical Care Society conference in 2012 as part of her Emergency/Critical Care residency requirements and took the lead on data collection and manuscript generation. Dr. Brian Hardy performed the statistical analysis and participated in manuscript generation. The Journal of Veterinary Emergency and Critical Care has accepted this article with minor revisions.

In addition to the manuscripts presented here and the creation of the STAT group, I am honored to be leading a national effort through our specialty college (ACVECC, American College of Veterinary Emergency and Critical Care) to create a national veterinary trauma system. The members were initially a direct spin off from the STAT group who realized establishing infrastructure and resources in a more unified way across the country could allow for improved patient care, as well as the opportunity to create a trauma registry that could be utilized in future clinical research efforts. Since initial discussions in 2011, the group has expanded in membership to include critical care specialists from both private and university veterinary hospitals from all across the country, Canada and Australia. In September 2011, ACVECC formally created the Veterinary Committee on Trauma (VetCOT) of which I am the chair.

VetCOT Vision: Creation of a network of lead hospitals that seed development of trauma systems. These hospitals will work collaboratively to define high standards of care and disseminate information that improves trauma patient management efficiency and outcome. There is strong consideration for development of a trauma registry in the future.

Goals for creating a network of Veterinary Trauma Centers:

1. **Enhanced trauma patient care** (e.g., improved survival, reduction of co-morbidities and development of protocols to improve efficiency and outcomes)

2. **Research collaborations** (e.g., development of evidence based medicine protocols; evaluation of minimally invasive, cost-effective interventions; translational medical opportunities)
3. **Increased visibility** of our associations/colleges (ACVECC, VECCS, AVECCT, VECCS, ACVS).
4. **Marketing advantages** to designated veterinary trauma centers in regards to the surrounding veterinary and general public populations.

This body of research and creation of two working groups regarding trauma patient research and care delivery (STAT, VetCOT, respectively) are a direct result of experiences obtained during Clinical Research Masters course work and collaborations with multiple enthusiastic, intelligent and supportive individuals. Additional research projects are already enrolling patients, and continued significant contributions to the veterinary literature, as well as continued efforts to have naturally occurring trauma in dogs contribute to improvements in human trauma care, are underway.

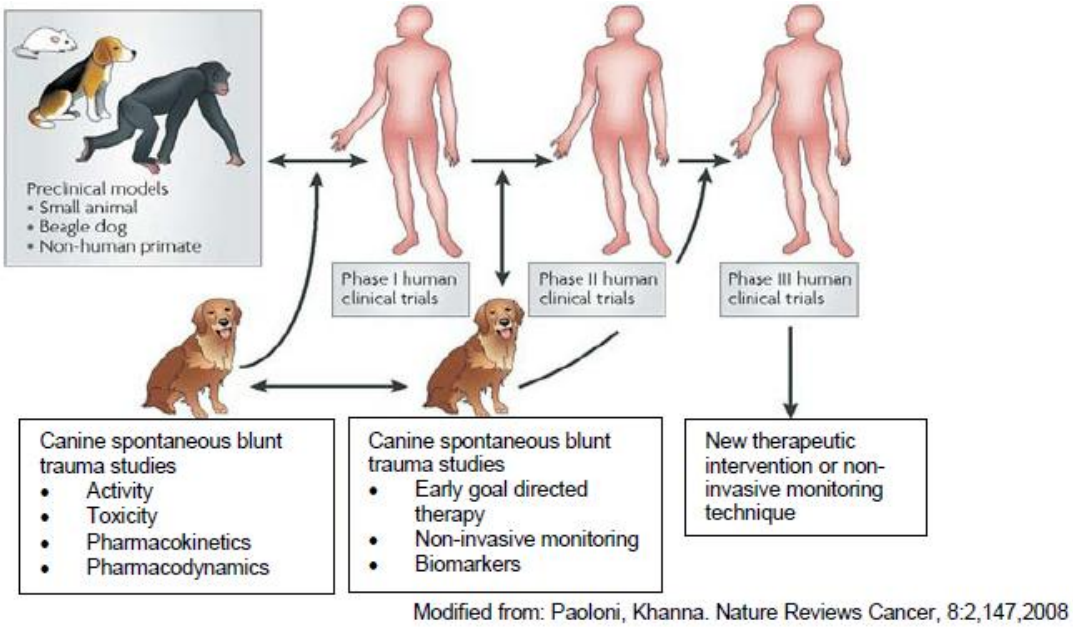

Figure 1: Spontaneous Trauma in Animals Team (STAT) concept

Project #1:

Title: Naturally occurring canine trauma: A model for early and late causes of human trauma morbidity and mortality

Hall KE, Sharp CR, Adams CR, Beilman G

In human blunt trauma patients, early deaths result from hemorrhage and brain injury, whereas late deaths are the result of multi-organ failure (MOF) and sepsis. A variety of experimental animal models, including several species, have been developed to investigate the pathophysiology of traumatic injury. Similar to other experimental models, these trauma models cannot recapitulate conditions of naturally occurring trauma, and therefore therapeutic interventions based on these models are often ineffective. Pet dogs with naturally occurring traumatic injury represent a novel translational model for human trauma that could be used to assess novel therapies. Large scale, retrospective veterinary clinical reports of dogs with traumatic injury highlight the similarities between canine and human blunt trauma. The American College of Veterinary Emergency and Critical Care Veterinary Committee on Trauma has initiated the development of a national network of veterinary trauma centers to enhance uniform delivery of care to canine trauma patients. Additionally, the Spontaneous Trauma in Animals Team, a multi-disciplinary, multicenter group of researchers have created a clinical research infrastructure for carrying out large-scale clinical trials in canine trauma patients. Moving forward, these national resources can be utilized to facilitate multicenter prospective studies of naturally occurring canine trauma to evaluate therapies and interventions that have shown promise in experimental animal models, thus closing the

critical gap in the translation of knowledge from experimental models to humans, and increasing the likelihood of success in Phase I and Phase II human clinical trials.

Introduction:

Trauma is defined as tissue injury that occurs more or less suddenly and includes physical damage to the body caused by violence or accident.(1) Trauma is a major cause of morbidity and mortality in both human and veterinary patients.(2-4) In fact, unintentional injury, generally secondary to motor vehicle accidents, is the most common cause of death for individuals under the age of forty-five.(5) Each year over 45,000 people in the United States alone die from motor vehicle accidents, and almost 2.5 million people are injured resulting in medical costs of over $625.5 billion dollars annually.(6)

Trauma-related mortality is trimodal, with most deaths occurring either prior to admission, early after hospital admission (within 48 hours), or late in the course of hospitalization (days to weeks following trauma). Most early trauma deaths are due to exsanguination/hemorrhagic shock (with blood loss of greater than 30% of blood volume) and central nervous system injury, while late deaths are the result of sepsis and/or multiple organ failure (MOF).(7) Recent epidemiologic data indicates that early mortality attributable to exsanguination has decreased dramatically over the last decade in people (from 25-15%) with the advent of the advanced trauma life support concept (ATLS®) in rescue systems, changes in resuscitation strategies, early goal-directed therapy in the emergency room, and improvements in hospital diagnostics, surgical techniques, and ICU care. Unfortunately however, there has been little change in mortality attributable to the later stage complications of polytrauma.(7,8) As such, it is

imperative that ongoing research be directed to furthering our understanding of the pathophysiology of these late stage complications and the development of novel interventions to improve outcome beyond patient stabilization in the emergency room. Despite advances in the management of trauma patients over recent decades, the morbidity and mortality that occur secondary to trauma remains unacceptably high. While translational research will remain the motor of medical advancement in trauma, there are growing barriers between clinical and basic science; in particular government regulations and financial constraints that make translation challenging.(9,10) Given that naturally occurring trauma in dogs mimics trauma in people, the use of a naturally occurring canine model has the potential to bridge this bench to bedside gap, while benefiting both the human and veterinary trauma patient.(3)

The objective of this paper is to compare the clinical and pathophysiologic human and veterinary literature regarding trauma as an introduction to the potential utility of spontaneous canine trauma as a model of human trauma.

Animal models currently used:

Much of the current body of information regarding the body's response to trauma has been elucidated in experimental rodent models.(11) Some large animal models involving dogs, sheep and pigs have also been evaluated. Early trauma models tended to involve a single insult such as hemorrhage (with or without fluid resuscitation), surgical laparotomy, head injury,(12) femur fracture,(13) or isolated, blunt lower limb trauma. More recent models have combined two insults (so called "two-hit models") with the aim

of better mimicking naturally occurring trauma in people,(11) but even these models are far from replicating human trauma.

In hemorrhage models, animals are bled to a predetermined blood volume, arterial blood pressure, cardiac output or another physiologic endpoint.(14) Subsequently, fluid administration may be performed to create reperfusion injury, as would occur in the clinical setting. While this controlled hemorrhage creates a somewhat reproducible model and is sufficient alone to induce hyperinflammation and immunosuppression, it fails to mimic the clinical situation because injured patients rarely suffer from isolated hemorrhagic shock.(15) Acceptance of these limitations has led researchers to combine hemorrhage with tissue trauma, usually simulated by laparotomy. These combined hemorrhage plus trauma models have been demonstrated to intensify the hemorrhage-induced derangement of the immune system in both rats and mice.(15-18) Laparotomy plus pressure-controlled hemorrhagic shock is probably the best studied animal model of multiple trauma; however, even this is still far from the clinical situation since surgical laparotomy is not the common tissue injury in multiple trauma patients, nor is hemorrhage controlled in the clinical setting. Uncontrolled hemorrhage models are most similar to what happens in naturally occurring trauma, but results are highly variable.(11) Femur fracture has been used in place of surgical laparotomy, in combination with hemorrhagic shock, and all three insults have also been combined to result in an even more severe pattern of immune derangement.(19) Given the significant limitations of experimental animal trauma models, more clinically relevant models of human trauma are urgently needed. Much of the data generated in experimental animal models of

trauma has not translated well to the clinical realm for many reasons, including the fact that experimental animals are anesthetized during the manipulations. The success of human clinical trials has therefore been compromised. Naturally occurring canine trauma is very similar to the syndrome in people, making dogs potentially an ideal model for human trauma.

The naturally occurring canine model:

Trauma is a common cause of morbidity and mortality in dogs. While there is not yet a national database for veterinary patients, traumatic injuries involving dogs are known to be a frequent cause for seeking veterinary care. Large-scale epidemiologic studies show that trauma accounts for approximately 11-13% of all cases presenting to urban veterinary teaching hospitals (4,20,21). A recent prospective multi-center study documented 315 consecutive canine trauma admissions during an 8-week period of time at four academic veterinary hospitals.(22) In a study evaluating causes of death in over 74,000 dogs, trauma was the second most common cause of death in juvenile and adult dogs, following infectious disease and neoplasia, respectively(23). More recent studies have documented many of the similarities in injury pattern and mechanism between humans and dogs sustaining trauma, including patient demographics (age and sex distribution), patterns and mechanisms of trauma, frequency of polytrauma, development of MOF and predictive capabilities of injury scores.(3,24,25) An added benefit to using naturally occurring canine trauma over experimental rodent models is that naturally occurring trauma in canine patients would be treated in a manner very similar to that of

human trauma patients; importantly, patients experiencing real-life injuries would not be experimentally anesthetized when undergoing injury and treatment.

Similarities in human and canine trauma morbidity and mortality (Table 1)

Age- and gender-specific responses: Similar to the patient demographics seen in the human trauma literature,(14) dogs sustaining trauma are usually young to middle aged, and males predominate.(3,25) Additionally there is a significant subset of veterinary geriatric trauma patients, not unlike the human situation. This is of significance since it is well known that the nature of the inflammatory response varies according to age and sex. In human medicine it is widely accepted that elderly patients have increased morbidity and mortality associated with trauma. However, the reasons for this are largely unknown,(11) and currently there are few studies attempting to understand the mechanisms of systemic insults, such as trauma, in aged individuals. The National Trauma Institute has urged translational studies that focus on "the extremes of age" in a long list of traumatic injuries.(10) Naturally occurring canine trauma presents an attractive approach to studying this demographic, as 9% (22/239) of canine trauma patients were geriatric in a recent review.(25) As with elderly human patients, these dogs had significant comorbidities including heart disease, endocrine disease (including diabetes mellitus), and chronic renal disease. Given the gross inadequacy of current experimental models for application to elderly human trauma patients, and the significant subset of geriatric dogs that sustain trauma, the canine model is particularly valuable.

It is well recognized that the immune response to trauma is gender-dimorphic since sex steroids play a decisive role in the depression or maintenance of immune function

following injury.(26) In particular, estrogen is thought to confer a protective effect since immunosuppression in trauma patients is most severe in young males, ovariectomized females, and aged females.(26) The beneficial effects of estrogen and the deleterious effects of testosterone have been demonstrated experimentally with the use of gonadectomized animals as well as by treating animals with hormonal agonists and antagonists in trauma-hemorrhage models.(26) However, despite a wealth of recent literature in this field, more studies are needed to understand the precise mechanisms of the beneficial effects of estrogen. Dogs offer a unique opportunity to evaluate the effects of estrogen in trauma, in that we have a population of sexually intact female dogs that can be compared to ovariohysterectomized dogs and male dogs, and the effects of testosterone can be evaluated by comparing sexually intact male dogs to castrated male dogs.

Hypovolemic shock secondary to major bleeding is often seen in polytrauma and accounts for much of the early in hospital mortality in trauma.(7) Evidence of hypoperfusion and hypovolemia is common in dogs presenting for evaluation of trauma. In a recent retrospective study of canine trauma, the presenting median lactate concentration in dogs requiring ICU admission was 3.5 mmol/L; mild uncompensated metabolic acidosis was also common.(3) While most dogs are treated with intravenous crystalloids for fluid resuscitation, a number of patients also require administration of blood products, as is the case in human medicine. In the aforementioned retrospective study, packed red blood cells (pRBCs) and fresh frozen plasma (FFP) were administered during initial resuscitation in approximately 5% of cases. A significant number of dogs

also required blood products later in hospitalization; overall 57/235 (24%) and 66/235 (28%) received pRBCs and FFP respectively. In that study most patients were fluid responsive and only 3 required vasopressor support.(3)

Thoracic injury: Dogs and humans have similar incidences of thoracic injury. In human medicine, 42% of polytraumatized patients have therapy-relevant findings on thoracic imaging,(27) and chest injuries account for 20-30% of trauma-related deaths.(28) In dogs, the most common thoracic injuries are pulmonary contusions (38.7%,(29) 44%(30), 58%(3)) and pneumothorax (17.5%(31), 21%(32), 24%(29), 47%(3)). Also seen are hemothorax, rib fractures, pneumomediastinum, diaphragmatic herniation, and flail chest.(3,29,33,34).

Abdominal injury: Abdominal injury is also common in both dogs and people sustaining blunt trauma. Abdominal injury accounted for 6.9% of reported traumatic injuries in 2010.(28) Hemoperitoneum is reported commonly in dogs after blunt trauma, with prevalence ranging from 23%(3) to 38%.(32) Urinary tract rupture (2(32)-3(3)%) and abdominal hernias (5%) occur in fewer dogs but are nonetheless significant and require surgical intervention.(3)

Point of care ultrasound (e-FAST exam) allows for the detection of free intra-peritoneal, pelvic, pericardial and pleural fluid as well as pneumothorax and can be completed in < 5 minutes with an overall accuracy of 90-98% for clinically significant intra-abdominal traumatic injuries in people.(35) Similarly, point of care ultrasound is considered standard of care in veterinary medicine improving efficiency and appropriate intervention in traumatized patients.(36) In one prospective study, 27% of canine trauma patients

presented with evidence of free abdominal fluid and patients with a higher FAST score (fluid in ≥3 of 4 sites evaluated) had an increased need for blood transfusion.(37)

Orthopedic injury: Dogs and humans also share orthopedic injury as a significant cause of morbidity and potential mortality. The epidemiology of orthopedic injury in people with polytrauma is poorly described, although likely significant. One author documented that about 20% of the polytrauma patients in their hospital undergo damage control orthopedic surgery.(38) A large number of dogs experience orthopedic injuries as well, with common injuries including pelvic fracture (28%), femur fracture (16%), hip luxation (12%), distal limb fracture (8%), spinal fracture (10%), sacral luxation (9%), and sacral fracture.(3) Less common but still seen in dogs are thoracic limb orthopedic injuries including scapular fracture (7%), elbow luxation (3%) and radius fracture (2%).(3)

Head injury: In human medicine, head injury and traumatic brain injury (TBI) account for 40-60% of trauma-related deaths.(39-42) Hyperglycemia, is particularly problematic in people and animals with head trauma.(43,44) Traumatic brain injury is often evaluated in isolation in experimental models, but TBI as part of a polytrauma syndrome is considerably more complex to manage, requiring a more clinically relevant model. Head injury occurs commonly in dogs and is associated with significant morbidity and mortality.(45-50)

Multiple organ failure: Like people, dogs sustaining trauma develop a systemic inflammatory response, and this response underlies the development of MOF. Both canine and human trauma patients usually present with fever, tachycardia, tachypnea and leukocytosis.(3,8,51,52) Likewise, in both species the cytokine storm in the early

proinflammatory state following trauma results in increased plasma concentrations of inflammatory mediators. Various studies in human medicine have documented increased concentrations of tumor necrosis factor alpha (TNF-α), Interleukin (IL)-1β, IL-6 and chemokine ligand (CX-CL8).(53) Preliminary studies have also documented increased circulating concentrations of pro-inflammatory cytokines (TNF, IL-6 and CX-CL8) in dogs with trauma induced systemic inflammation.(54)

Other organ dysfunctions of significance that can occur as a result of SIRS and have been documented in human and veterinary trauma patients include metabolic, renal, hepatic and gastrointestinal dysfunction.(25,55-58)

Lung injury, in its most severe form manifesting as acute respiratory distress syndrome (ARDS), is one of the most frequent and severe sequela in people with post-traumatic systemic inflammatory response syndrome (SIRS). In SIRS, ARDS is precipitated by the cytokine storm, which damages alveolar epithelial and endothelial cells and is associated with an influx of activated neutrophils and protein-rich fluid into the alveoli.(57) Diffuse alveolar damage not only impairs gas exchange, but also reduces endogenous protective mechanisms such that these patients are at increased risk of developing pneumonia. In a large, prospective cohort study evaluating 4,020 human blunt trauma patients, 12% developed ARDS and the development of ARDS was associated with dramatically higher mortality (20% compared to 11.9% in patients without ARDS). Older people are also more likely to develop and succumb to ARDS following trauma.(59) Acute respiratory distress syndrome is also a recognized complication in veterinary trauma patients.(25,60) A recent retrospective study documented ARDS in 3% of patients (7/235). In addition to

these dogs, another 2 dogs in that study required mechanical ventilation due to the severity of pulmonary injury.(3) Only 1 of those 9 ventilated dogs survived to discharge, highlighting the potential for lung injury to contribute to late stage mortality in canine trauma patients. Survival rates for dogs ventilated for management of pulmonary contusions in another study was slightly higher (30%). While not discussed specifically, it appears that these dogs could be considered to have had ARDS based on a mean+/- standard deviation PaO_2:FiO_2 ratio of 77.49+/-24.8 prior to ventilation.(60)

The **coagulation system** is activated concurrently with inflammation in the setting of severe trauma. Trauma results in vascular endothelial damage, resulting in exposure of tissue factor that initiates the coagulation cascade. There is also tight interplay between inflammation and coagulation such that each perpetuates the other. In addition to upregulation of procoagulant pathways, endogenous anticoagulants (such as antithrombin and protein C) are depleted. Both hyper- and hypo-coagulability have been described in trauma patients,(61,62) with up to 85% experiencing a hypercoagulable state.(63) A recent systematic review of the coagulopathy of trauma looked for relevant experimental models with which to study early traumatic coagulopathy concluded that there is an utter lack of relevant models and calling for models that more closely resemble human physiology.(64) Dogs and humans experience similar hemostatic changes associated with other inflammatory conditions, particularly sepsis,(65-71) therefore, dogs are a promising naturally occurring model of this post-traumatic coagulopathy.

At this time there is no consensus definition of posttraumatic coagulopathy, and we are far from understanding its highly complex pathophysiology.(72,73) The correlation

between traditional laboratory tests of coagulation and clinical signs of hemorrhage or thrombosis is poor. Conventional coagulation parameters, such as the prothrombin time (PT) and partial thromboplastin time (PTT) are inadequate alone to interpret a patient's coagulation status. Thromboelastography is increasingly common and provides a more global evaluation of coagulation and a guide to transfusion therapy in hemorrhage.(74) In veterinary medicine there is a paucity of current literature describing the coagulopathy of trauma. A large retrospective canine study documented mild PT prolongation (25-50% greater than control) in 13.2% and mild PTT prolongation in 30.2% of cases.(3) Moderate PT prolongation (50-100% greater than control) was observed in 7.5% of dogs, and moderate PTT prolongation in 13.2%. An abstract presented on a more recent prospective study evaluating 40 canine traumatic injuries documented hypocoagulability in more severely injured dogs.(75) To the knowledge of the authors, there are no published reports objectively documenting hypercoagulability in veterinary trauma patients. Additional veterinary studies are required to elucidate the role of dysregulated coagulation in veterinary trauma.

Scoring systems and clinical management. A variety of trauma scoring systems are used in human medicine, of which the Trauma and Injury Severity Score (ISS) is the most widely accepted.(28,76) As in human medicine, scoring systems are used in veterinary medicine for patient stratification. The animal trauma triage (ATT) score has been statistically validated in dogs and cats,(77) and has been correlated with survival in multiple subsequent retrospective studies.(3,25) The Glasgow coma scale (GCS) score has also been validated for use in dogs. (46) These scoring systems will allow

comparison of injury severity between study centers and of treatment effects across different subgroups of injury.

Available canine clinical research infrastructure.

A multi-disciplinary, multi-institutional group: Spontaneous Trauma in Animals Team (STAT) has been created with a primary goal to improve trauma patient outcome through comparative and translational medicine. The group's first project enrolled 315 consecutive canine trauma cases at four centers over an 8-week period of time utilizing a web-based data capture system.(78) Blunt trauma (motor vehicle accident, fall) occurred most commonly (55%) followed by penetrating (34%, gun shot wound, animal interaction, etc.) and unknown (11%) trauma. A majority of the animals (91%) survived to discharge. Admission variables including injury severity scores [Animal Trauma Triage (ATT, range 0-18), Modified Glasgow Coma Score (MGCS, range 3-18)] and lactate were associated with non-survival [ATT score ≥ 5 (AUC 0.91), MGCS ≤ 17 (AUC 0.87), lactate ≥ 4.0 (AUC=0.79)]. Surgery was required in 50% of the cases with a majority (70%) being soft tissue procedures, 28% orthopedic procedures and 3% requiring neurologic surgery.(22) The STAT infrastructure has been designed in anticipation of performing future intervention studies. Study execution, expertise and resources for current and future projects will be provided by the *site investigator working group* made up of veterinary critical care specialists, a *data monitoring/advisory committee* made up of human trauma surgeons, epidemiologist, biostatistician and veterinary critical care specialists and individual center *veterinary clinical research organizations* (e.g., Clinical Investigation Center, University of Minnesota) which

provide research coordinators and clinical research technicians to ensure efficient study logistics. All centers involved require Institutional Animal Care and Use Committee (IACUC) approval for clinical research on client owned animals. Informed client (pet owner) consent with IACUC approved consent forms are required for all veterinary clinical research projects performed at veterinary teaching hospitals.

The concept of evaluating naturally occurring diseases in dogs to enhance human patient care has become more prevalent in recent years, particularly in the fields of oncology(79), epilepsy(80) and gene therapy(81). All of these areas have successfully obtained NIH funding to advance the care of humans and animals, alike. Regarding trauma research, specifically, the opportunities to evaluate light weight, effective and practical interventions for severely traumatized soldiers (and occasionally their working dogs) is a driver for many government funded projects (DoD, USSOCOM); in fact, some of the military government agencies have funding available specifically for canine trauma studies (USSOCOM). Finally, veterinary trials in other areas (e.g., oncology, spinal injury, etc.) have obtained funding from industry partners and private companies interested in interventional trials that are inserted as pre -Phase I or Phase II human clinical trials guiding "go/no go" decisions. The infrastructure provided by the STAT group will maximize the ability to facilitate and carry out intervention studies sponsored by the government, industry and foundation partners, alike.

In addition to the clinical and translational research driven STAT group, the American College of Veterinary Emergency and Critical Care Society (the veterinary critical care specialty college) has created the Veterinary Committee on Trauma (VetCOT) which has

established Guidelines for Veterinary Trauma Centers (https://sites.google.com/a/umn.edu/vetcot/) and is creating a network of lead hospitals that seed development of trauma systems. These hospitals will work collaboratively to define high standards of care and disseminate information that improves trauma patient management uniformity, efficiency and outcome. The VetCOT is also developing a canine trauma registry to allow a large database of information that will be accessible to clinical researchers.

Conclusions:

The clinical management of canine trauma patients presenting to tertiary referral hospitals, such as the authors' institutions, is very similar to that in human medicine. While pre-hospital treatment in veterinary medicine is generally very limited, most patients are seen by a primary veterinarian within a short interval after the trauma. Emergency room treatment is very similar, involving intravenous fluid resuscitation from shock, administration of blood products, emergency diagnostics, imaging as needed, and screening blood work. These similarities in patient management will allow data gathered in a canine model of naturally occurring trauma to have translational application. A limiting factor in delivery of available clinical resources to clinical canine trauma patients is cost of care. The option to pet owners for euthanasia in veterinary medicine is a difference in clinical patient approach; however, because many similar clinical resources are available to the patient, investigation of interventions through funded clinical trials would help minimize this factor. Additional study design and statistical methods can be employed to minimize the impact of this factor, as well.

The canine trauma model offers an opportunity to leverage information learned from experimental canine trauma models in concert with information from naturally occurring canine trauma models that occur in the clinical setting. From this, we can gain a better understanding of the physiologic alterations that occur during traumatic injury and the subsequent development of SIRS, sepsis and MOF. Prospective, multicenter studies at high volume veterinary medical centers would enable interventional trials that could be inserted as pre-Phase I or Phase II human clinical trials to guide "go/no go" decisions for groups developing therapeutic strategies to improve outcome for human trauma patients thereby benefiting human and veterinary patients, alike.

	Human	Canine
Age and gender	Mostly young – middle aged males(14) Need for studies in "extremes of age"(10) Evidence of estrogen protective effects, unknown mechanism(26)	Mostly young – middle aged males(3,25) Geriatric population with co-morbidities (9%)(25) Population of intact and gonectamized animals for hormonal comparisons (3)(4,20,25)
Hypovolemic shock	Cause of early hospital mortality(15)	Median lactate at admission 3.5 mmol/L(3) Most cases crystalloid fluid responsive(3) Use of blood product (pRBCs 24%, FFP 28%)(3)
Thoracic injury	Overall incidence 10.7%(28) Therapy relevant thoracic injuries in polytrauma patients: 42%(27) Trauma-related deaths: 8.6%(28)	Pulmonary contusions (38.7-58%)(3) (29,30) Pneumothorax (17.5-47%)(3,29,31,32) Other injuries: hemothorax, rib fractures, pneumomediastinum, diaphragmatic herniation, flail chest.(3,29,33,34)
Abdominal injury	Overall incidence 6.9%(28) Incidents with AIS≥3: 6.3%(28) Trauma-related deaths: 7.8%(28) Point of care ultrasound (e-FAST) for rapid detection of fluid and air(35)	Common injuries: Hemoperitoneum (23%(3) -38%(32)) Urinary rupture (2%(32) -3(3) %) Abdominal hernia (5%)(3) Point of care ultrasound (A-FAST, T-FAST, C-FAST) for rapid detection of fluid and air(36)
Orthopedic injury	Epidemiology poorly described Reported: 20% of the polytrauma undergo damage control orthopedic surgery(38)	Fractures and luxations: 87%(4) Common injuries: Pelvic fracture (28%), femur fracture (16%), hip luxation (12%), spinal (10%), distal limb (8%), sacral luxation (9%),

		scapular fracture (7%), elbow luxation (3%), radius fracture (2%)(3)
Head injury	Overall incidence 17.6(28) Incidents with AIS≥3: 35%(28) Trauma-related deaths: 40-60% (39-42) Hyperglycemia associated with head trauma(43)	Head injuries common; associated with significant morbidity and mortality (45-50) Hyperglycemia associated with head trauma(44)
SIRS/Multiple organ failure	Present with fever, tachycardia, tachypnea and leukocytosis(8,51,52) Increased concentrations of TNF-α, IL-β, IL-6 and CX-CL8(53) Metabolic, renal, hepatic and gastrointestinal dysfunction reported(55-58)	Present with fever, tachycardia, tachypnea and leukocytosis(3) Increased concentrations of pro-inflammatory cytokines(54) Metabolic, renal, hepatic and gastrointestinal dysfunction reported(25)
Lung injury	12% developed ARDS(59)	3% developed ARDS(3)
Coagulation system	Acute Coagulopathy of Trauma-Shock well described; interventions being studied(72)	13.2% cases mildly prolonged PT and 30.2% with mildly prolonged PTT(3) 7.5% cases moderately prolonged PT and 13.2% with moderately prolonged PTT(3) Hypocoagulability associated with more severe injury and poorer outcome(75)
Scoring systems	Trauma and Injury Severity Score (TISS)(28,76) Glascow Coma Scale Score	Animal trauma triage score (ATT)(77) Modified Glascow Coma Score (mGCS) validated in dogs(46)

Table 1: Trauma epidemiology: Human and canine comparison

Project #2:

Title: A multi-center eight-week prospective cohort study of 315 dogs sustaining trauma

Kelly E. Hall, DVM, DACVECC; Marie K. Holowaychuk, DVM, DACVECC; Claire R. Sharp, BSc, BVM(Hons), MS, DACVECC; Erica Reineke, VMD, DACVECC

The co-authors are representatives of the "Spontaneous Trauma in Animals Team", a multi-institutional, multi-discipline group collaborating to improve trauma patient outcome through comparative and translational medicine.

From the Departments of Veterinary Clinical Sciences (Hall), College of Veterinary Medicine, University of Minnesota (UMN), St. Paul, MN 55108; Department of Clinical Studies (Holowaychuk), Ontario Veterinary College (OVC), University of Guelph, Guelph, ON N1G 2W1, Canada; Department of Clinical Sciences (Sharp), Tufts University, Cummings School of Veterinary Medicine, North Grafton, MA 01536; Department of Clinical Studies (Reineke), University of Pennsylvania (UPenn), Philadelphia, PA 19104. Dr. Hall's present address is Veterinary Clinical Sciences Department, University of Minnesota, 1352 Boyd Avenue, St. Paul, MN 55108.

The authors thank Brianna Hallman, Jessica Marder, Molly Racette, Erin Flath, Randie Schinzel (UMN); Meagan Walker and Tiffany Jagodich (OVC); Jennifer Savini (UPenn); and Jillian Morlock, Nahvid Etedali, Monika Burns (Tufts) for their assistance with data collection and Gabrielle Monteith (OVC) for assistance with statistical analyses.

Study data were collected and managed using REDCap electronic data capture tools hosted at University of Minnesota. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.(Harris, PA)

Address correspondence to Dr. Kelly Hall at wilke022@umn.edu

Objective: To characterize admission variables in dogs sustaining trauma with emphasis on scoring systems (Animal Trauma Triage (ATT), Modified Glasgow Coma Scale (MGCS), and Acute Patient Physiologic and Laboratory Evaluation (APPLE) scores) and their ability to predict outcome.

Design: Prospective, multicenter, cohort study

Animals: 315 client-owned dogs

Procedures: Using a web-based data capture system (REDCap), trained personnel prospectively recorded admission ATT, MGCS, and APPLE scores, clinical and laboratory data, and outcome from dogs presenting following trauma to four veterinary teaching hospitals.

Results: Blunt trauma occurred most commonly (173/315, 54.9%) followed by penetrating (107/315, 34.0%) and unknown (35/315, 11.1%) trauma. 90.5% (285/315) of dogs survived to hospital discharge. When dogs euthanized due to cost were excluded (16/315, 5.1%), dogs with blunt trauma were less likely to survive, compared to dogs with penetrating trauma (P=0.021, OR=0.118). ATT (median 2, range 0-14, P<0.001) and MGCS (median 18, range 3-18, P<0.001) scores at admission were predictive of outcome. Lactate was recorded in 118 dogs (median 2.0, range 0.6-14.0 mmol/L) and was a risk factor for non-survival (P=0.005, OR=1.488). Surgical procedures were performed in 49.8% of dogs and were predictive of survival to hospital discharge (P=0.006, OR=7.092). Sex (female 43.5%, male 56.5%), age (median 3.5, range 0.15-16.3 years), body weight (median 11.8 kg, range 1.0-60.4) and body condition score (median 5, range 3-9) were not associated with outcome.

Conclusions and Clinical Relevance: ATT and MGCS scoring systems are useful to predict non-survival following trauma in dogs. Penetrating trauma, decreased admission blood lactate, and performance of surgical procedures during hospitalization predicted survival to hospital discharge in this population.

Introduction

Trauma, defined as tissue injury that occurs more or less suddenly and includes physical damage to the body caused by violence or accident,[1] is a common cause of morbidity and mortality in dogs. Large-scale epidemiologic studies show that trauma accounts for approximately 11-13% of all cases presenting to urban veterinary teaching hospitals. [2,3] In a recent study evaluating causes of death in over 74,000 dogs, trauma was the second most common cause of death in juvenile and adult dogs, following infectious disease and neoplasia, respectively.[4] Multiple large retrospective studies have documented the injury pattern, as well as clinical and laboratory variables in dogs sustaining trauma including patient demographics, mechanism of trauma, frequency of polytrauma, development of multiple organ failure, and prognostic indicators.[2,5-8] Predictors of non-survival in dogs determined retrospectively include cardiac arrhythmias, body wall hernias, severe soft tissue injuries, head trauma, vertebral fractures, and recumbency at hospital admission.[5,6]

Scoring systems have also been investigated in dogs following trauma and have both clinical and research applications. From a clinical standpoint, scoring systems can be incorporated into protocols developed to improve triage, guide therapeutic and diagnostic interventions, or benchmark performance.[9] In clinical research, scoring systems can be used to measure effectiveness of randomization and facilitate patient stratification in order to decrease bias and confounding variables.[9] The Animal Trauma Triage (ATT) score was validated in a small population of dogs and cats and has been associated with survival in multiple subsequent retrospective studies.[5,6,10,11] In a retrospective study of

dogs with head trauma, the Modified Glasgow Coma Scale (MGCS) score predicted a 50% non-survival rate within 48 hours of the injury.[12] Most recently, the Acute Patient Physiologic and Laboratory Evaluation (APPLE) score was validated as a user-friendly scoring system for dogs admitted to an intensive care unit.[3]

While previous veterinary studies have investigated different variables and scoring systems on hospital admission after trauma, they have been retrospective in nature or limited to single-center populations of dogs. The objective of the present multi-center study was to prospectively characterize admission variables in dogs sustaining trauma with particular emphasis on scoring systems (ATT, MGCS, and APPLE scores) and their ability to predict outcome. We aimed to achieve this using a multi-center consortium and online database to secure the framework and collaborative mechanisms required for future multi-center prospective clinical trials investigating canine trauma patients.

Materials and Methods

Trained personnel at four veterinary teaching hospitals (University of Minnesota Veterinary Medical Center, Tufts University Foster Hospital for Small Animals, Ontario Veterinary College Health Sciences Center, University of Pennsylvania Ryan Veterinary Hospital) prospectively recorded information from all dogs presenting after a witnessed or suspected traumatic incident between June 27, 2011 and August 22, 2011. Trauma was defined as any tissue injury that occurred more or less suddenly as a result of an external force including but not limited to: blunt force injury (e.g., motor vehicle accident, fall from height), penetrating injury (e.g., gunshot, laceration, impalement, animal altercation,

porcupine quills), or crushing injury. Dogs were excluded if they presented for acute lameness highly suspected or ultimately determined to be a cruciate ligament rupture, non-traumatic acute paresis (e.g., intervertebral disc disease, fibrocartilaginous embolism) or minor superficial bite wounds limited to 1 limb. Standard owner consent regarding data use from the medical record was obtained at hospital admission.

Data was transcribed to a paper worksheet and then entered into an online database (REDCap)[13] and retrospectively verified with the completed medical record. The following variables were recorded for each dog: ATT score,[10] MGCS score,[12] age, sex, body condition score (BCS), body weight, time and cause of the injury, veterinary care prior to arrival, whether or not the trauma was witnessed, pre-existing medical conditions, blood product administration, performance of cardiopulmonary resuscitation (CPR), total cost of the visit, as well as the number and type (soft tissue, orthopedic, or central nervous system) of surgical events (which may have included 1 or more surgical procedures) and surgical procedures (defined as surgical repair of tissues in one region) performed and where they took place (Emergency room (ER) or operating room (OR)). Time from injury to hospital admission was calculated and cause of the injury was further categorized into one of three groups: blunt (e.g., motor vehicle accident, fall, other), penetrating (e.g., bite wounds, penetrating non-bite wounds), or unknown. Age was also categorized as young, middle, or old with correction for body weight.[14] For dogs discharged from the hospital after the initial trauma visit that returned for trauma-associated wound management, the total cost of the visit was only recorded for the initial

visit; however, surgical procedures were included in the number of surgeries if they were a result of the initial traumatic injury.

Additional data was recorded if obtained at the discretion of the attending clinician including: values for calculation of the APPLE score (i.e., serum creatinine, albumin, and total bilirubin, blood lactate concentration, white blood cell count (WBC), pulse oximetry (SpO_2), mentation score, respiratory rate, and fluid score)[3] and Focused Assessment using Sonography for Trauma (FAST) Abdominal Fluid Score (AFS).[15] Outcome was recorded as survived to hospital discharge, euthanized, or died. Time of death was recorded and categorized into < 2, 2-6, 6-12, 12-24, 24-72 or > 72 hours after presentation to the hospital. For dogs that were euthanized, information regarding the reason (cost vs. grave prognosis) was also recorded after speaking with the attending clinician. Dogs euthanized for financial reasons were excluded from outcome analyses.

Statistical Analyses

Continuous variables were analyzed for standard normal distribution with a Shapiro Wilk test. Descriptive statistics were recorded as mean and standard deviation (normal distribution) or median and range (non-normal distribution). Depending on normal distribution, a Pooled Student or Wilcoxon Mann-Whitney test was used to assess differences in the mean or median for clinical and laboratory parameters between surviving and non-surviving dogs. Univariate exact conditional logistic regression was used to assess categorical variables including sex, age category, trauma category, previous illness, surgery, blood product administration, positive fluid score or FAST

AFS, and whether or not the trauma was witnessed as risk factors for non-survival. Univariate exact conditional logistic regression was also used to assess continuous variables including age, BCS, body weight, time from injury to hospital admission, MGCS score, ATT score, serum albumin, serum total bilirubin, serum creatinine, lactate, SpO_2, WBC, and total cost of the visit as risk factors for non-survival. Receiver operating characteristic (ROC) curve analysis was performed to determine the area under the curve (AUC) and select the optimum cut-off value that maximized the Youden's J statististic (sensitivity + specificity-1) for sensitivity and specificity reporting. Data analysis was performed by use of computer software (SAS OnlineDoc 9.1.3, SAS Institute, Cary, NC). A P-value < 0.05 was considered significant for all comparisons.

Results

Animals – Data was initially recorded for 327 dogs. Twelve dogs met exclusion criteria and were censored: single small puncture wound to an extremity (n=6), chronic orthopedic disease or anterior cruciate ligament rupture (n=4), chemical burn (n=1) and hemivertebrae causing spinal cord injury (n=1). Data analysis was performed on the remaining 315 dogs enrolled at Tufts University (107/315, 34.0%), University of Pennsylvania (101/315, 32.1%), University of Minnesota (73/315, 23.2%), and Ontario Veterinary College (34/315, 10.8%). Female dogs (137/315, 43.5%) were mostly spayed (95/137, 69.3%) and male dogs (178/315, 56.5%) were mostly castrated (109/178, 61.2%). Dogs were categorized when possible (312 dogs) as young (208/312, 66.7%),

middle-aged (81/312, 26.0%), and old (23/312, 7.4%). Of the dogs, 52 (16.5%) were being treated for a previous illness.

Trauma – Causes of trauma included motor vehicle accidents (94/315, 29.8%), bite wounds (84/315, 26.7%), falls (57/315, 18.1%), other (35/315, 11.1%), unknown (25/315, 7.9%), penetrating non-bite wounds (12/315, 3.8%), and porcupine quills (9/315, 2.9%). Blunt trauma (173/315, 54.9%) occurred most commonly, followed by penetrating (107/315, 34.0%), and other (35/315, 11.1%) trauma. Trauma was witnessed for 220 (69.8%) of dogs and 217 (70.7%) dogs presented within 24 hours of the injury.

Treatments and Procedures – Some dogs (101/315, 32.1%) presented to another veterinarian prior to hospital admission where treatment included crystalloids (35/101, 34.7%), colloids (2/101, 2.0%), hypertonic saline (4/101, 4.0%), steroids (10/101, 9.9%), non-steroidal anti-inflammatory drugs (NSAIDs) (30/101, 29.7%), or both steroids and NSAIDs (2/101, 2.0%). A surgical event was required in 157 (49.8%) of dogs that had a total of 164 surgical events. Most dogs required only 1 surgical event (151/157, 96.2%); however, 6 dogs (3.8%) required 2 or more surgical events. Eight-four (84/164, 51.2%) surgical events were performed in the ER and 80 (48.8%) surgical events were performed in the OR. A total of 174 surgical procedures were performed including 114 (65.5%) soft tissue surgical procedures, 55 (31.6%) orthopedic surgical procedures, and 5 (2.9%) CNS surgical procedures. A FAST was performed in 37/315 (11.7%) of dogs, the majority of which were negative (32/37, 86.5%). A fluid score was recorded in 54/315 (17.1%) of dogs and was 0 in most of the dogs (42/54, 77.8%). Only 7/315 (2.2%) of dogs received

blood products (n=3 plasma, n=1 packed red blood cells, n=3 plasma and packed red blood cells).

Outcome – 285 (90.5%) of dogs survived to hospital discharge. Of the 30 dogs that did not survive, 5 dogs (16.7%) died, 9 dogs (30.0%) were euthanized for a grave prognosis, and 16 dogs (53.3%) were euthanized for financial reasons. Of the 30 non-survivors, 19 deaths were within 2 hours of presentation to the hospital (3 died, 16 euthanized), 5 were euthanized 2-6 hours after presentation, 3 were euthanized 12-24 hours after presentation, and 1 was euthanized and 2 died 24-72 hours after presentation. CPR was performed in 5 dogs (1.6%) and none of those dogs survived to discharge (4 died, 1 euthanized).

Scoring Systems and Prognostic Indicators – APPLE score was only calculated for 13 dogs (4.1%) due to insufficient data available in the medical record, whereas ATT (312/315, 99.0%) and MGCS (310/315, 98.4%) scores were calculated for almost all dogs. ATT score (P<0.001, OR 2.0, CI 1.6-2.7), MGCS score (P<0.001, OR 0.47, CI 0.30-0.69), and blood lactate concentration (P=0.005, OR 1.5, CI -1.1-2.0) were predictive of non-survival (Table 1). Blunt trauma, when compared to penetrating trauma, was more likely to result in non-survival (P=0.021, OR 8.5, CI 1.2-333.3) as 92.9% (13/14) of non-surviving dogs sustained blunt trauma, compared to 53.0% (151/285) of surviving dogs (Table 2). Requirement for surgery was predictive of survival (P=0.006, OR 7.1, CI 1.5-66.7) as 54.4% (155/285) of surviving dogs had surgery, whereas only 14.3% (2/14) of non-surviving dogs had surgery (Table 2). Other laboratory and clinical

variables including sex, BCS, age, age category, previous illness, blood production administration, presentation to another veterinarian first, time from injury to admission, whether or not the trauma was witnessed, and total cost of the visit were not predictive of survival (Tables 1 and 2).

ROC curve analysis – The usefulness of blood lactate concentration, MGCS score, and ATT score for predicting non-survival were evaluated using ROC curve analysis. A lactate ≥ 4.0 mmol/L predicted non-survival with 80% sensitivity and 56% specificity (AUC=0.785). A MGCS score ≤ 17 predicted non-survival with 82% sensitivity and 87% specificity (AUC 0.913). ATT score was the best predictor of mortality; an ATT score ≥ 5 predicted non-survival with 83% sensitivity and 91% specificity (AUC 0.913).

Discussion

In this multicenter population of canine patients, blunt trauma (54.9%) was the most common cause of injury, followed by penetrating (34%) and unknown injury (11.1%). There was an overall 90.5% survival to discharge and 8% of the animals were euthanized (poor prognosis (2.9%) and financial reasons (5.1%)). Higher ATT score and blood lactate levels and lower MGCS score predicted non-survival. Patients sustaining penetrating trauma (vs. blunt trauma) and those requiring surgical intervention were more likely to survive to discharge. A majority of animals were young (66.7%) and male (56.5%).

The ATT score evaluates 6 categories (perfusion, cardiac, respiratory, eye/muscle/integument, skeletal, and neurologic) on a scale of 0-3 (0: little to no injury;

3: severe injury; total range 0-18), and is easy to use with little requirement for data beyond physical exam findings and radiographic detection of fractures.[10] As with previous retrospective and single-center studies, ATT score was associated with outcome ($p<0.001$) and strongly predictive of non-survival.[6,10,11] With an ATT score ≥ 5 having 83% sensitivity and 91% specificity for predicting non-survival to discharge (AUC=0.913), this large prospective study validates the utility of this score in canine trauma patients.

The MGCS score was previously evaluated retrospectively in dogs sustaining blunt head trauma to assess for traumatic brain injury and determine the score's ability to predict outcome.[12] The score evaluates 3 categories (motor activity, brain stem reflexes, level of consciousness) on a scale of 1-6 (6: little to no abnormalities, 1: severe abnormalities) with a total score possible ranging from 3-18. The score is also easy to calculate using only physical exam findings. In the present study, the MGCS score was associated with outcome ($p<0.001$) and a score ≤ 17 predicted non-survival with 82% sensitivity and 87% specificity (AUC=0.87). This finding is consistent with previous studies that have found head trauma to be a negative prognostic indicator for survival.[5,12] Unfortunately, the MGCS score has its limitations as evidenced during the study when assigning a score to dogs with spinal cord injuries. Because these dogs had altered motor activity, but often no evidence of traumatic brain injury, they were assigned a lower MGCS score than other non-head injured dogs. Further consideration regarding the best method for applying MGCS score to dogs with spinal cord injury may be warranted in larger scale trials.

In order to calculate the APPLE score, nine data points are required from each dog: serum creatinine, albumin, total bilirubin and lactate, WBC, SpO_2, mentation score, respiratory rate, and fluid score.[3] Although the score was created from a population of hospitalized dogs using values obtained within the first 24 hours of admission, the present study attempted calculation of the score using variables from traumatized dogs available at presentation. As this was an unfunded study and tests required for calculation of the APPLE score were performed at the discretion of the primary clinician, only 13 dogs (4.1%) had enough data available to calculate the APPLE score. Future investigation of the APPLE score in dogs following trauma might confirm its prognostic ability and enable stratification of dogs in subsequent analyses based on disease severity.

Because scoring systems are developed from populations of dogs, caution must be exercised when using each dog's individual score to assist owner decisions regarding whether or not to pursue therapy. More appropriate uses of the individual scores might instead include decision-making during triage or determining the resources required for patient care. For example, an ATT score > 5 may require activation of a trauma team or an MGCS score < 17 may necessitate involvement of a neurologist. Similarly, a dog with a higher ATT score might require longer hospitalization, requirement for surgical intervention, and a higher estimated cost of care, all important client communication points at patient presentation. From a clinical research perspective, scoring systems can be utilized for patient screening and study enrollment, as well as reducing bias in multi-arm clinical trials. The ease with which ATT and MGCS scores can be calculated at

admission, as well as their association with outcome, suggests that this data be recorded as part of a minimum data base on all trauma cases.

Elevated blood lactate levels have been documented in canine patients in multiple disorders including shock, low cardiac output states, acute liver failure, severe sepsis, neoplasia, seizures, poisoning, and drug therapy.[16] Most analyzers that measure lactate levels require a very small volume of blood, and are typically available as a bedside diagnostic test, making it an easily accessible parameter to inform patient care. In this population of dogs, elevated lactate levels were associated with non-survival with a lactate level ≥ 4.0 mmol/L having 80% sensitivity and 56% specificity (AUC=0.785) for non-survival. While single time point lactate level has prognostic capabilities in this population, it is recognized that lactate clearance may be a better method for predicting outcome and guiding therapy in hyperlactatemic patients.[16]

Blunt trauma, defined as motor vehicle accident, fall or crush injury, was the most common cause of injury in the present study population (54.9%) and is slightly lower than previously reported in a large retrospective population (61.7%).[2] Similar to other studies, motor vehicle accident was the most common cause of blunt trauma.[2,5] Penetrating injuries (34%) were more common than previously described (23.3%)[2] and bite wounds made up the majority of penetrating wounds (26.7%). Conversely, bite wounds comprised only 10.2% of injuries in a previous general canine trauma population.[2] Differences in the distribution of types of injuries that occurred in previous studies could be explained by differences in geography, time of data collection, and

definition of trauma between studies. Kolata et al. included burn (1.3%) injuries and was a single site retrospective study of 1000 dog and cats, whereas Simpson et al. retrospectively evaluated only dogs sustaining blunt trauma at a single teaching hospital.[2,5]

In this population, blunt injury was more likely to result in non-survival when compared to penetrating injury (P=0.021, OR 8.5, CI 1.2-333.3). There is sparse veterinary literature regarding penetrating injury patterns in small animals, and no large population description of survival patterns in dogs. Animal interaction (10.2%), sharp object (11%) and weapon (2.1%) injuries are described in the canine population (203/871, 23.3%) reported in Kolata's 1974 study, but survival data for this subpopulation of penetrating injuries is not reported.[2] A 1997 study evaluated 84 cats and dogs with gunshot wounds and reported an 80.5% survival to discharge, compared to an 85-88% survival to discharge noted in blunt trauma literature.[2,5,6,17] As this is the first report of a survival advantage in canine penetrating injury (when compared to blunt trauma), further validation in additional large-scale trials as well as further evaluation into differences in severity scores, resources utilized, hospital time and therapies required are necessary to better explain this finding.

Surgical intervention occurred in approximately half (49.8%) of the dogs in the present study, similar to that reported in a large population of severe blunt trauma patients (50%).[5] Interestingly, the distribution of soft tissue versus orthopedic injuries was reversed: 65.9% soft tissue procedures in the current study versus 36.5% in the Simpson

study, and 31.6% orthopedic procedures in the current study versus 63.5% previously reported (Simpson 2009).[5] In this study, requirement for surgery was associated with survival (P=0.006, Table 2) with a significant odds ratio of 7.1 (CI 1.5-66.7). While definitive explanation for this finding is unknown, it is possible that owner willingness to pursue therapy (including surgery) in the population of surviving dogs (vs. electing to euthanize due to cost of surgical fixation) may influence this finding. Alternatively, perhaps increased monitoring (many surgeries require hospitalization) and pain control contributed to the higher survival rate in this sub-population of patients.

A secondary objective of this study was to obtain population data to plan future clinical research and trials in canine trauma. The overall survival to discharge rate in this study (90.5%) was slightly higher than previously reported in large populations (85-88%).[2,5,6,8] There are many possible reasons for this, including the prospective design of the present study, which likely captured less severe cases that would have been missed in a retrospective record review, as well as inclusion of all types of trauma (i.e., penetrating, blunt and other). Given the high survival to discharge rate in this population of animals, future intervention studies aimed at improving outcome in this population of animals may require consideration for alternative primary outcomes, e.g., decreased frequency of co-morbidities (e.g., development of multiple organ failure, coagulopathic bleeding, etc.), length of hospital stay, and cost of care. This initial study has demonstrated the feasibility of tracking a limited number of epidemiologic data points at multiple centers in order to inform future intervention study design and track resource use for local centers.

One persistent challenge in veterinary clinical research is the influence of euthanasia on clinical studies. During this prospective study, efforts were made to document the estimated cost and prognosis provided to owners by attending clinician at the time of euthanasia. This additional data was obtained in order to more accurately exclude cases euthanized due to cost from analysis (vs. interpreting reason for euthanasia from retrospective review of medical record). One challenge in recording this data surrounded the prognosis given for spinal injuries; while the prognosis for survival to discharge recorded for many of these dogs was good, prognosis for return to function was not recorded and may have influenced owner decision. In future trauma studies, prognosis for return to function for patients with brain or spinal injury should be recorded, in addition to prognosis for survival to discharge. Unfortunately, euthanasia confounded evaluation of timing of death from presentation. Most animals (19/30) died or were euthanized within 2 hours of presentation to the hospital, 16 of which were euthanized (84%). Of the patients that died (5/30), 3 were within 2 hours of presentation and 2 were 24-72 hours after presentation. Although the numbers are too small to draw definitive conclusions, this distribution is somewhat similar to human trauma mortality where by a majority of patients die within hours of their trauma, and an additional "spike" in mortality is noted days later.[18]

In this multi-center, prospective population of canine trauma cases, ATT and MGCS scores, blood lactate concentrations, need for surgical intervention and type of injury (blunt v. penetrating) were associated with outcome. Overall survival to discharge was excellent. The present study successfully established a multi-center collaborative group

that used a secure web-based data-capture system{{ 178 Harris,Paul A. 2009;}} to enable collection of data from a large group of dogs during a short time period. Although there was significant investment in volunteer time and many individuals to obtain data on all cases presenting to each site over an 8-week period of time, the ability to obtain data on > 300 cases in a relatively short period of time (8 weeks) supports the use of similar collaborations and data capture systems to enable future, large-scale clinical trials investigating trauma in veterinary medicine.

Table 1: Clinical and laboratory variables from surviving and non-surviving dogs following trauma.

	Survivors			**Non-survivors**			
	N	**Mean ± SD**	**Median (Range)**	**N**	**Mean ± SD**	**Median (Range)**	**P-value**
Age (years)	283	4.1 ± 3.6	3.3 (0.2-16.3)	14	5.2 ± 3.6	4.8 (0.8-15.0)	0.238
BCS	214	5.3 ± 1.1	5 (3-9)	7	5.7 ± 1.0	6 (4-7)	0.420
Body weight (kg)	275	17.2 ± 13.5	12.0 (1.0-60.4)	10	19.5 ± 14.6	16.0 (3.5-42.9)	0.598
Time from injury to hospital presentation (days)	278	1.4 ± 6.7	0 (0-98)	13	0.5 ± 1.4	0 (0-5)	0.655
Time from injury to rDVM presentation (days)	88	0.8 ± 4.4	0 (0-41)	7	0 ± 0	0 (0)	0.396
MGCS score	**283**	**17.8 ± 0.7**	**18 (10-18)**	**11**	**15.3** ± 3.4	**17 (6-18)**	**<0.001**
ATT score	**284**	**2.1 ± 1.7**	**2 (0-9)**	**12**	**7.9 ± 3.9**	**8.5 (2-14)**	**<0.001**
Albumin (g/dL)*	54	3.1 ± 0.7	3.0 (1.7-4.5)	5	3.0 ± 0.9	2.9 (1.9-4.3)	0.772
Bilirubin (mg/dL)	50	0.2 ± 0.2	0.2 (0-0.9)	5	0.1 ± 0.1	0.1 (0.1-0.2)	0.377
Creatinine (mg/dL)	121	1.0 ± 0.7	0.9 (0.4-6.4)	8	1.1 ± 0.5	1.0 (0.6-2.0)	0.299
Lactate (mmol/L)	**106**	**2.8 ± 1.9**	**2.0 (0.6-10.6)**	**5**	**6.5 ± 5.2**	**4.5 (2.0-14.0)**	**0.005**
SpO2 (%)	30	95.2 ± 6.2	97 (72-100)	2	94.5 ± 0.7	94.5 (94-95)	0.605
WBC ($\times 10^3$/ μL)	56	14.2 ± 5.6	13.7 (4.9-28.6)	5	10.7 ± 3.3	12.8 (6.2-13.4)	0.168
Cost ($) USD	285	1491.53 ± 2213.00	586.00 (37.10-21865.40)	14	1393.00 ± 1598.14	449.00 (120.00-4961.29)	0.869
LOH (days)	284	1.5 ± 2.3	1 (0-21)	14	0.7 ± 1.1	0 (0-3)	0.208

BCS – body condition score; rDVM – referring veterinarian; MGCS = Modified Glasgow Coma Scale; ATT = Animal Trauma Triage; APPLE – Acute Patient Physiologic and Laboratory Evaluation; SpO_2 – pulse oximetry; WBC – white blood cell count; USD = United States Dollars; LOH – length of hospitalization *Normally distributed

Table 2: Proportions of categorical variables from surviving and non-surviving dogs following trauma.

	Survivors	**Non-survivors**	**P-value**
Witnessed trauma	35.1% (100/285)	71.4% (10/14)	1.000
Previous illness	17.9% (51/285)	7.1% (1/14)	0.530
Surgery performed	**54.4% (155/285)**	**14.3% (2/14)**	**0.006**
Blood product administered	2.1% (6/285)	7.1% (1/14)	0.575
Visited rDVM prior to arrival	25.2% (72/285)	50.0 % (7/14)	0.255
Blunt trauma	**53.0% (151/285)**	**92.9% (13/14)**	**0.021**

Project #3:

Title: Tissue oxygen saturation (StO_2) in dogs presenting for acute hemorrhage

Hall, K and Gray S (Co-first authors), Brearley A, Schildt J, Powell L, Beilman G

Objective – To evaluate initial tissue oxygenation (StO_2) readings in dogs presenting to the Emergency Room (ER) for acute hemorrhage. It was hypothesized that ER measured StO_2 levels would differentiate levels of shock.

Design – Prospective, observational study

Setting – Veterinary teaching hospital

Animals – Thirty-eight dogs with acute hemorrhage and 78 healthy dogs

Interventions – Tissue oxygen readings were obtained at enrollment on patients presenting to the ER for acute hemorrhage. Baseline clinicopathologic (CBC, chemistry, PT/PTT) and physiologic (lactate, blood gas, blood pressure, SpO_2) data were documented on all patients. An ER clinician blinded to StO_2 readings guided patient management and resuscitation. Patients were followed to determine survival to discharge status. Once data collection was complete, three emergency/critical care clinicians blinded to the StO_2 data retrospectively classified patients into 1 of 4 shock categories (no shock, mild, moderate or severe).

Measurements and Main Results – Thirty-eight patients were enrolled. Seventy-eight patients from a previous observational study in normal dogs were included to represent shock level 1 ("no shock"). The "no shock" category (1) StO_2 levels differed significantly from the other three categories (mild, moderate and severe, p-values: 0.0006, <0.0001

and 0.0018 respectively); however, there was no statistical difference in pairwise tests between the other levels (mild, moderate, severe).

Conclusions – In canine patients, StO_2 levels as measured by near-infrared spectroscopy are able to differentiate a population of canine patients in hemorrhagic shock from those without perfusion abnormalities.

Acknowledgements - Philippe Gaillard (BDAC statistician)

Introduction

A primary goal, and challenge, for veterinarians that care for urgent and emergent patient populations is the early identification of patients that are in shock. Shock is defined as inadequate cellular energy production and clinically this leads to tissue hypoxia. Near-infrared spectroscopy (NIRS) is emerging as a technology that may help clinicians not only identify patients with occult shock,[1-3] but aid in directing therapy to resuscitate such patients (e.g., early goal directed therapy)[4-6] by measuring oxygen saturation at the level of the tissues.

The InSpectra™ Tissue Spectrometer[a] is a portable, non-invasive, continuous data output NIRS device that measures tissue hemoglobin oxygen levels (StO_2) when placed over a muscle body.[1] Having established normal StO_2 levels (93±7%) in healthy dogs with this device,[7] the next reasonable step is to determine if StO_2 correlates well with the parameters currently used in veterinary medicine for determining shock.[8] StO_2 levels in human trauma patients have been shown to perform similar to base excess (BE) in predicting development of multiple organ dysfunction or death.[9] In models of hemorrhagic shock in the pig, StO_2 levels showed excellent correlation with global oxygen delivery[10] and were a significant predictor of mortality when compared with conventional measures.[3]

The purpose of this study is to determine if StO_2 measurements can differentiate a population of normal dogs from a population of canine patients that have presented to the

emergency room (ER) for acute hemorrhage. We hypothesize that ER measured StO_2 levels will differentiate levels of shock (none, mild, moderate or severe) in the hemorrhage population. This study is modeled directly from a human study that evaluated this tool for identifying patients in occult shock.[2]

Materials and Methods

The study protocol was reviewed and approved by the Institutional Animal Care and Use Committee (IACUC), and informed consent was obtained from the owner of each dog enrolled.

Acute hemorrhage population: Canine patients presenting to the University of Minnesota emergency room ER with evidence of acute hemorrhage between July 2009 and October 2010 were enrolled. Exclusion criteria included inability to obtain access to the sartorius or digital extensor muscle bodies for tissue oxygenation readings or owner refusal to have their pet enrolled. Following enrollment, investigators obtained StO_2 and tissue hemoglobin index (THI) readings from either the sartorius or the digital extensor muscle during a 2-5-minute interval after enrollment while the patient was in the ER and receiving clinician directed therapy. The clinician managing the patient was blinded to StO_2 readings. When obtaining StO_2 readings, an attempt was made to use sites without pigmentation. If pigmentation was noted, an estimated amount of pigmentation where the probe was placed was recorded (0, <25%, 26-50%, 51-75%, >75%). Patient positioning during readings was also recorded.

At the time of StO_2 measurement, patient vitals (temperature, pulse, respirations) were recorded. Additional data obtained at enrollment included blood lactate,[b] blood pressure (Dinamap or Doppler),[c,d] blood oxygen saturation (SpO_2) via pulse oximetry,[e] arterial blood gas,[f] complete blood count,[g] chemistry profile,[h] prothrombin time and partial thromboplastin time.[i] Patient demographics including age, sex, neuter status and weight were recorded. Finally, time in ER, hospitalization time, survival to discharge, diagnosis and hospital bill were also recorded.

Once data collection was complete, patients were retrospective classified by emergency/critical care specialists (KH, LP, JS) blinded to StO_2 data into 1 of 4 shock classifications. Two clinicians performed the classification individually, and a third criticalist was used as a tiebreaker if the level of classification differed. If all three criticalists disagreed, then a discussion of the case was performed and a consensus determined. Classification levels used were as follows: Level 1: no shock- patients with no tachycardia, hypotension, normal BE, and minor or insignificant co-morbidities; Level 2: mild shock-patients with mild tachycardia, no hypotension, normal BE, and only minor co-morbidities; Level 3: moderate shock - patients with hypotension, tachycardia responsive to fluid resuscitation, decreased BE, and major co-morbidities. Level 4: severe shock patients-severe hypotension, marked tachycardia, decreased BE, and severe co-morbidities.

Level 1 (no shock): As no animals presenting for acute hemorrhage were classified as no shock, the data from a previous study evaluating 78 normal canines StO_2 values[7] were utilized as level 1.

Statistical Analysis

Because the tissue oxygen levels were not normally distributed, the StO_2 levels in the four shock categories and the StO_2 levels in the three outcome categories (survival to discharge, died or euthanized) were compared using the non-parametric Kruskal-Wallis rank sum test. Pair-wise tests were conducted to determine which categories differ, using the Kruskal-Wallis test but adjusting for multiple comparisons (alpha= 0.05/6 = 0.0083). Additionally, using linear regression, the association of StO_2 to time in hospital and cost of stay was determined. A receiver operating characteristic (ROC) curve was used to determine the area under the curve (AUC) and

select the optimum cut-off value that maximized the Youden's J statistic (sensitivity + specificity-1) for sensitivity and specificity reporting. For the purposes of sensitivity and specificity reporting, dogs without shock (level 1) were considered true negatives and dogs with shock (levels 2-4) were considered true positives. A p value of less than 0.05 was considered significant. All analysis was done in SAS 9.2.[j]

Results

Between July 2009 and October 2010 there were a total of 39 dogs that were assessed for enrollment that met inclusion criteria for the acute hemorrhage population. Only one dog that was assessed by investigators that met inclusion criteria was excluded due to lack of

client consent. The remained 38 dogs were enrolled and included in the analysis. The median age was 8.5 years (range 0.58-13.58 years). There were 20 females and 18 males enrolled; of the females, 2 were intact and remainder were neutered; of the males 3 were intact, and the remainder were neutered. The median weight was 29.1kg (range: 4.1-53.6kg). There were 7 Labrador Retrievers (or mixes), 5 Golden Retrievers (or mixes), and 4 German Shepard Dogs (or mixes). The remaining breeds were not represented more than twice. The most common cause of hemorrhage was secondary to an intra-abdominal mass (n= 20). Other causes of hemorrhage included vehicular trauma (n=5), penetrating trauma (n=3), gastrointestinal hemorrhage (n=3), pericardial effusion (n=2), coagulopathy (n=2), other penetrating injury (n=1), and unknown etiology (n=2).

Thirty (79%) of the initial StO_2 readings were obtained from the sartorius muscle body and eight (21%) from the digital extensor muscle body. Twenty-three (61%) of the initial readings were performed with the patient in lateral recumbancy and 15 (39%) were obtained with the patient in sternal recumbancy. Degree of pigmentation on the skin was noted in 37/38 patients with no pigmentation in 17/37 (46%), 1-25% pigmentation noted in 17/37 (46%), 26-50% pigmentation noted in 1/37 (3%), and > 50% pigmentation noted in 2/37 (5%). The median THI readings (an indicator of signal strength) were 11.4 (range 4-20.6), 8.3 (range 2.6-15.9), 12.4 (single value) and 11.9 and 15.9 (2 values), in the categories of no pigmentation, 1-25%, 26-50% and > 50%, respectively.

The median StO_2 values (range) were 94% (56%-99%), 89% (34%-94%), 84% (23%-94%), and 83% (63%-94%) for levels 1 (no shock), 2 (mild shock), 3 (moderate shock) and 4 (severe shock) respectively (Table 1, Figure 1). The distribution of StO_2 in shock category 1 (no shock) differs significantly from that the other three categories (p-values 0.0006, <0.0001 and 0.0018 respectively); the remaining pair-wise differences are not significant (p-values 0.3607, 0.6050 and 0.9227). When StO_2 values with a THI≤5 were removed from analysis (3/78 in no shock group, 2/15 in mild shock group and 2/15 in moderate shock group), the distribution of StO_2 in shock category 1 (no shock) remained significantly different from that the other three categories (p-values 0.0018, <0.0001 and 0.0008 respectively); the remaining pair-wise differences also remained not significant (p-values 0.2804, 0.2456 and 0.6370). StO_2 values (range) with THI≤5 readings removed are listed in Table 1 and presented in Figure 2. ROC curve analysis for shock status as a function of StO_2 revealed an AUC=0.824 (Figure 3). Patient vitals, biochemical data and patient outcome by shock code are also reported in Table 1.

Of the 38 clinical patients enrolled, no patients were categorized as a level 1; there were 15 categorized as level 2, 15 categorized as level 3, and 8 categorized as level 4. Blinded clinician agreement on shock categorization was present in 26 cases. Nine cases had different classification on initial independent review, and were classified based on agreement between 2 of 3 reviewers after independent review by the third clinician. There were 3 cases for which there was no independent agreement as to level of shock and all three reviewers openly discussed those cases and a consensus was determined.

The overall survival rate of the acute hemorrhage group was 63.2% (n=24). Of the non-survivors, 2 died and 12 were euthanized. Based on medical record review, 7 patients were euthanized due to quality of life issues and 5 patients were euthanized due to progression of their disease. In this population of patients the initial presenting StO_2 value was unable to predict survival (p-value 0.3866). The median duration of hospitalization was 21.5 hours (range 1-140 hrs) and the median cost of hospitalization was $1916.50 (range $914-14,432). There was no correlation found between StO_2 levels at presentation and hospital stay or cost of hospitalization (P=0.3).

Discussion

The primary purpose of this study was to determine if tissue oxygen levels, as measured by the InSpectra™ Tissue Spectrometer,[a] is able to differentiate a population of normal dogs from a population of dogs with hemorrhagic shock presenting to the emergency room, as well as compare initial (presentation) tissue oxygen levels with clinician assessment of degree of shock. The current study was modeled after a previous study whereby degree of shock in a population of human trauma patients was determined by a panel of three traumatologists and compared to StO_2 levels.[2] The normal reference interval for human StO_2 is 87%±6.[1] In the Crookes paper, the StO_2 levels were 83%±10, 83%±10, 80%±12 and 44%±26 in the no shock (n=98), mild shock (n=19), moderate shock (n=14) and severe shock (n=14) populations, respectively, with significant differences reported between normal and all 4 classifications of shock, as well as

significant differences between severe shock and all other categories ($p < 0.05$). In our study, StO_2 readings were significantly different between the normal population of dogs and each of the shock levels, respectively, but did not reach statistical significance in differentiating the various clinician determined levels of shock; however, there is evidence of a trend of lower StO_2 readings as the level of shock increases (Figure 1). These conclusions persist when StO_2 values with a THI<5 are removed from analysis (Table 1, Figure 2).

In the initial study evaluating StO_2 readings in normal dogs, the sartorius muscle body was the most consistent sight for obtaining readings (100%).[7] In the current study, initial StO_2 readings were always attempted at the sartorius muscle, but if THI levels were < 5 and/or a reading was not obtained within 60 seconds, the investigator moved to the digital extensor muscle. It is unclear why obtaining readings from the sartorius muscle in this population of dogs was less consistent than the normal population. One possibility could be amount of time in recumbancy prior to obtaining readings. In human medicine, vascular occlusion testing (VOT) utilizing the tissue oxygen monitor has been investigated as another method for determining patient perfusion.[11] In this scenario, a cuff is used to occlude blood flow to the limb for a short period of time, and the degree with which StO_2 readings rebound is evaluated as an assessment of perfusion. All readings obtained in the normal population of dogs and the hemorrhage population of dogs were obtained in either sternal or lateral recumbancy; however, due to clinical status, the

hemorrhage population may have been in recumbancy for a longer period of time, effectively decreasing blood flow to the dependent limb where readings were attempted.

In the hemorrhage population, obtaining readings from regions where there was little to no skin pigmentation present was attempted based on subjective findings that pigmentation may affect ability to obtain a reading.[1,7] In humans, the THI is an indicator of signal strength, and StO_2 readings obtained with a THI level < 5 are not considered accurate.[1] A majority of the readings (92%) in the hemorrhage population were obtained from sites with minimal pigmentation (<25%); however, the 3 readings obtained from sites with >26% pigmentation had THI levels of 11.9-15.9 (considered a strong signal). Given the very small number of values obtained in patients with skin pigmentation, conclusions regarding degree of interference cannot be made; however, the authors still suggest obtaining readings where there is limited pigmentation until further studies evaluating degree of interference from pigmentation are pursued.

One of the goals for evaluating the ability for StO_2 levels to predict level of shock in patients is the immediate, non-invasive and continuous information that can be obtained with the device. In contrast, other shock parameters (lactate, base excess, blood pressure, cardiac output, etc.) either require blood sampling (delay in results being reported, non-continuous values) or invasive device placement (arterial line, pulmonary arterial catheter). The assignment of degree of shock was made by retrospective evaluation of prospectively obtained clinical data to ensure clinicians had the entire patient picture

available, including outcome. The ultimate goal being to determine if the immediate readings obtained by the tissue oxygen monitor were comparable to critical care specialists with access to all patient data points available for review (including those not available immediately). While the gold standard for sensitivity and specificity testing was the classification of degree of shock by three critical care specialists, it is recognized that this assignment still carries a degree of subjectivity, even with well-defined criteria for each level of shock, and this level of subjectively could results in mis-classification of cases. While not statistically significant, it is noted that StO_2 readings did trend toward lower values as the degree of shock level increased.

When utilizing survival to discharge as an outcome in clinical research, one of the persistent challenges in veterinary medicine is dealing with the fact that patients may be euthanized due to cost or perceived prognosis that may otherwise survive to discharge. In this particular study population, 12/38 (32%) of the hemorrhage patients were euthanized, making interpretation of StO_2 readings as a predictor of non-survival problematic. Additionally, duration and cost of hospitalization will be skewed for patients euthanized early in the course of treatment, also affecting statistical analysis of StO_2 readings at admission with those respective outcomes. Future studies which prospectively track reason for euthanasia may assist with more accurately determining if StO_2 levels predict outcome when animals definitively euthanized purely for cost are removed from statistical analysis.

There are a number of limitations in the current study. Firstly, there were no dogs in the hemorrhage population that were identified as “no shock”. This is likely due to the fact that evidence of hemorrhage was required for inclusion, and patients with gross evidence of hemorrhage will at least be in compensatory shock. Because client consent was required for enrollment in the study, one of the challenges noted by the authors were “missed cases” that were ultimately determined to be hemorrhaging, but diagnosis was delayed until after initial therapy and diagnostics due to low clinical suspicion of hemorrhage by the primary clinician.

These missed opportunities actual enhance the argument for utilization of StO_2 readings as a triage tool.

Another limitation is the degree of clinical difference between the populations. Because the hemorrhage population included only dogs with evidence of gross hemorrhage, those patients with occult shock were likely not included. Further evaluation of StO_2 levels measured on all patients presenting to the Emergency Room would expand the patient population and allow for more effective evaluation of the device’s ability to detect shock in a diverse patient population, including those in occult shock. Future studies evaluating this non-invasive, continuous read device will include evaluation of its application in other emergency room populations, as well as its used as an endpoint in early goal directed therapy.

In conclusion, StO_2 readings, as measured by the InSpectra™ Tissue Spectrometer, are able to differentiate a population of normal dogs from a population of dogs with hemorrhagic shock. In this population, StO_2 readings did not correlate statistically with degree of shock as assigned by critical care specialists, but as degree of shock increased, there was a trend in reduced StO_2 values in each of the shock populations.

Footnotes:

a. InSpectra Tissue Spectrometer, Hutchinson Technology Inc, BioMeasurement Division, Hutchinson, MN.
b. Accutrend lactate, Sports resource group, Hawthorne, NY
c. Parks Medical Model #811B, Parks Medical, Aloha, OR. (Doppler)
d. BCI Advisor, Smiths Group, London, England. (Dinamap)
e. Nonin Model #8500AV, Nonin Inc, Plymouth, MN. (SpO2 monitor)
f. i-STAT 1 analyzer, EG7 cartridge, Abbott Laboratories, East Windsor, NJ.
g. Cell-Dyn 3500, Abbott, Chicago, IL.
h. Olympus AU400, Olympus America Inc, Center Valley, PA.
i. STA Compact, Stago, Parsippany, NJ.
j. SAS version 9.2, SAS Institute, Inc., Cary, NC.

Variable	Shock code			
	1 (n=78)	2 (n=15)	3 (n=15)	4 (n=8)
StO_2 (%)	94 (56-99)	89 (34-94)	84 (23-94)	83 (63-94)
StO_2 (%), THI≤5 removed	94 (60-99) (n=3)	90 (66-94) (n=2)	85 (38-94) (n=2)	83 (63-94) (n=0)
Temperature (˚F)	101.7 (99.5-103.9)	100.9 (97.9-102.3)	101.3 (97-104)	99 (96-102.7)
Pulse (bpm)	110 (80-150)	150 (120-180)	140 (100-180)	170 (122-211)
pH	7.382 (7.310-7.459)	7.436 (7.345-7.460)	7.406 (7.316-7.485)	7.282 (6.962-7.390)
HCO_3^- (mmol/L)	20 (16.3-25.7)	20.8 (16.5-22.9)	16.9 (8.6-22.1)	12.6 (7.9-21.2)
BE (mmol/L)	-5 (3, -9)	-3 (-1, -9)	-8 (-2, -16)	-15 (-5, -18)
Lactate (mmol/L)	1.0 (0.4-3.0)	3.1 (0.7-5.2)	5.4 (2.3-10.3)	9.9 (8.5-12.7)
SBP (mmHg)	122 (85-180)	140 (90-182)	110 (53-168)	68 (46-111)
SpO_2 (%)	98 (92-100)	97 (88-100)	95 (89-100)	99 (95-100)
PT (sec)	NA	7.6 (6.7-120)	8.2 (6.9-14)	10.2 (8.4-86.3)
PTT (sec)	NA	13.5 (9.5-58.2)	15 (11-20.1)	16.3 (13.7-37.5)
Time in ER (min)	NA	145 (0-390)	122.5 (0-190)	142.5 (0=255)
Hospital time (hrs)	NA	25 (6-89)	21 (6-140)	4.5 (1-52.5)
Cost of stay ($)	NA	2005 (1208-6710)	1877 (1100-14432)	1687 (914-4515)
Survival (%)	78 (100%)	11 (73%)	10 (67%)	3 (38%)

Table 1: Values reported as median (range); StO_2=tissue oxygen saturation levels, HCO_3^- = bicarbonate, BE =base excess, SBP=systolic blood pressure, SpO_2=pulse oximeter oxygen saturation, PT=prothrombin time, PTT=partial thromboplastin time, ER=Emergency Room, Survival=survival to discharge

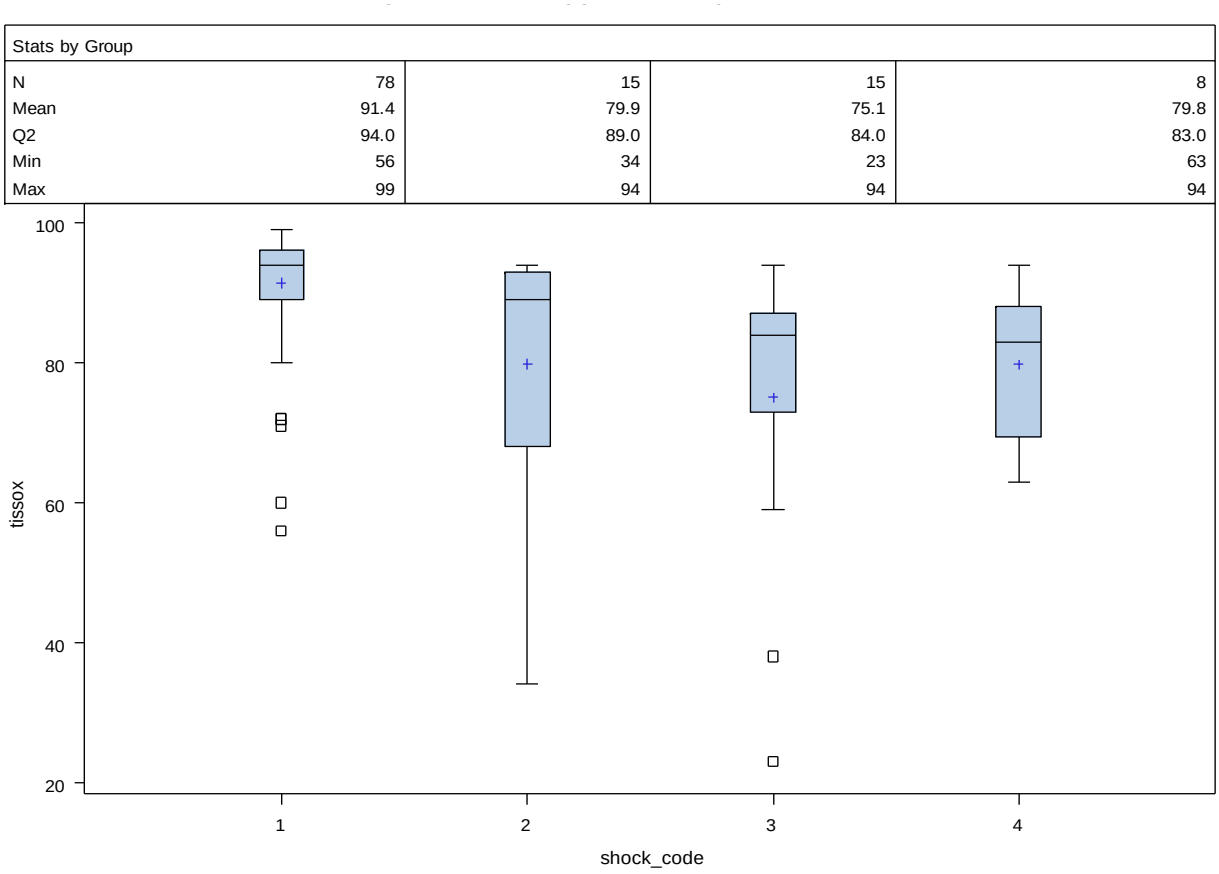

Figure 1: Tissue oxygen levels by shock category. Q2=median value; tissox=StO_2

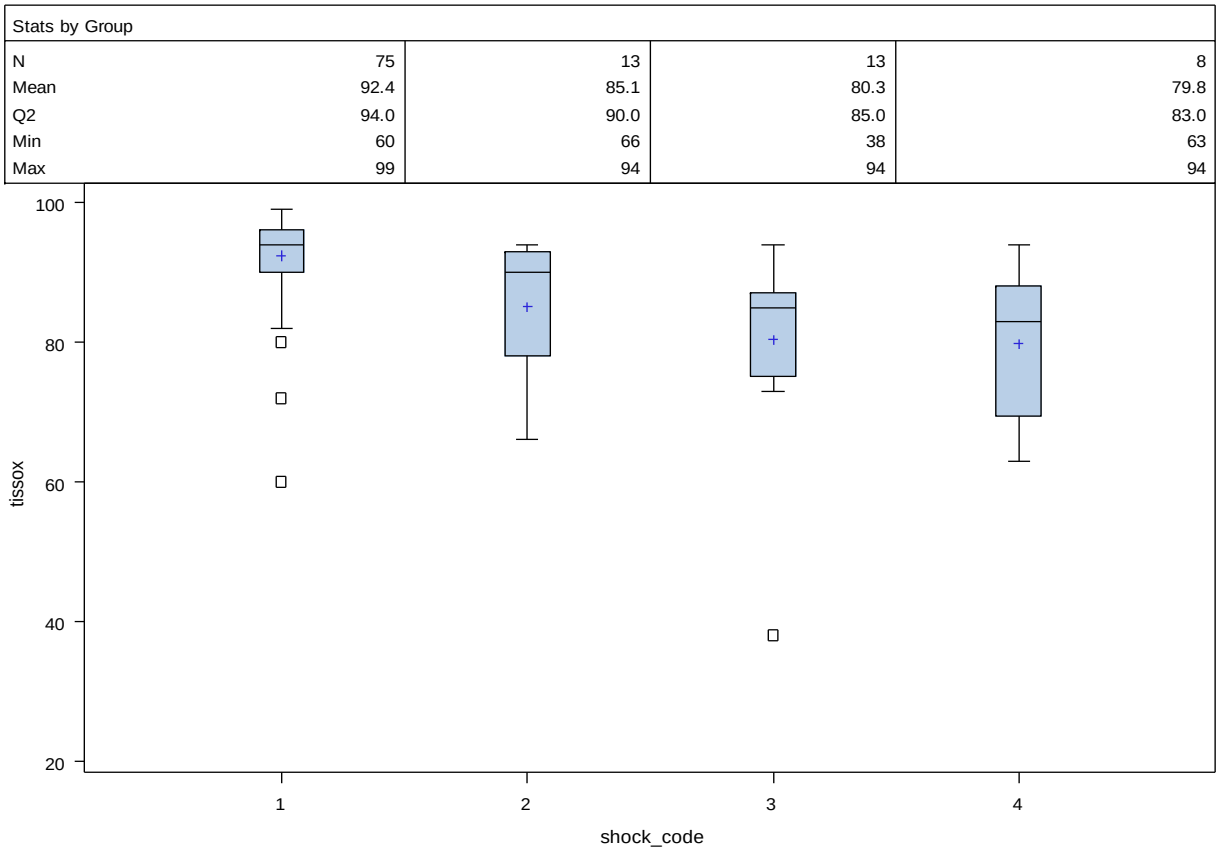

Figure 2: Tissue oxygen levels by shock category with THI ≤ 5 removed. Q2=median value; tissox=StO_2

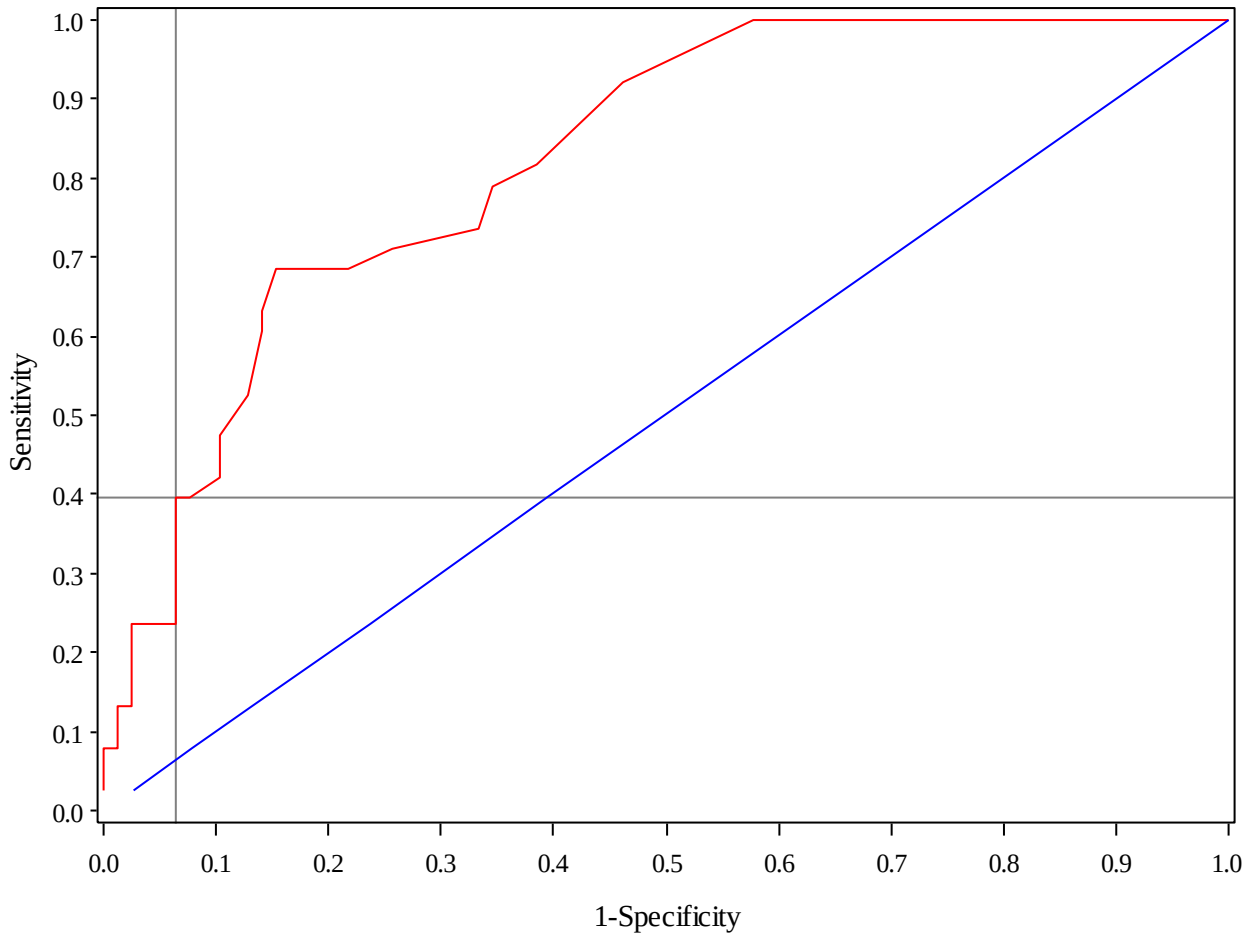

Figure 3: Receiver operating characteristic curve comparing the diagnostic sensitivity and 1-specificity of StO_2 for differentiating dogs without shock (Level 1) from dogs with shock (Levels 2-4). AUC=0.824

Project #4:

Title: Assessment of shock index in healthy dogs and dogs in hemorrhagic shock

Peterson K, Hardy B, **Hall KE**

Objective – Compare shock index in a population of healthy dogs to a population of dogs with confirmed hemorrhagic shock.

Design – Retrospective study using prospectively collected data from 2 previous studies

Setting - University teaching hospital

Animals – 78 healthy control dogs enrolled in a study to establish a reference interval for a tissue oxygen monitor; 38 confirmed hemorrhagic shock dogs enrolled in a study to evaluate the tissue oxygen monitor in hemorrhagic shock. The heart rate and systolic blood pressure obtained during the respective studies were used to calculate the shock index.

Interventions – None

Measurements and Main Results - Shock index was significantly higher in the hemorrhage group (median 1.37, range 0.78 to 4.35) than the control group (median 0.91, range 0.57 to 1.53); 92% of the hemorrhage dogs had a shock index of > 0.91. Hemorrhage dogs had significantly lower body temperatures (hemorrhage median 38.3°C, range 35.6 to 39.9°C; control median 38.7°C, range 37.5 to 39.9°C), higher heart rate (hemorrhage median 150 bpm, range 120 to 220 bpm; control median 110 bpm, range 80-150 bpm), lower systolic blood pressure (hemorrhage mean 112 mmHg, SD +/- 35.8 mmHg; control mean 125 mmHg, SD+/- 21.5 mmHg), higher lactate levels

(hemorrhage median 0.51 mmol/L, range 0.078 to 1.41 mmol/L; control median 0.11 mmol/L, range 0.033 to 0.33 mmol/L), and lower hemoglobin (hemorrhage median 81 g/L, range 56 to 183 g/L; control median 162.5 g/dL, range 133 to 198 g/L) than control dogs.

Conclusions: Shock index is a simple and easy calculation that can be used as an additional triage tool for emergency doctors and should prompt further investigation for hemorrhage if the value is above 0.9.

Key words: triage, emergency, heart rate, blood pressure

Abbreviations:

ER: emergency room

HR: heart rate

SI: shock index

SBP: systolic blood pressure

StO_2: tissue oxygen saturation

Introduction

Patients presenting to the emergency room (ER) in shock are common and the ability to recognize and characterize patients in shock continues to be a challenge for veterinarians. Vital signs such as heart rate (HR), respiratory rate, and blood pressure when evaluated alone often lack sensitivity and specificity and scoring systems are often cumbersome in the emergent setting. Shock index (SI) is a tool that can be utilized in the emergency room and is calculated by dividing HR by the systolic blood pressure (SBP), i.e., SI=HR/SBP. This calculation may provide a more objective measure of shock than HR and SBP alone, especially in patients with compensated or early hypovolemic shock and can be used in conjunction to clinician assessment of the patient's perfusion parameters.[1-3]

Shock index has been evaluated in people, with a normal range of 0.5 to 0.7.[1] It has been shown to correlate with acute blood loss in healthy donors[1] and may be a useful triage tool in patients with acute myocardial infarction,[4] trauma,[2,3,5] tubal or ectopic pregnancy,[6,7] ICU transfer,[8] community acquired pneumonia,[9-11] gastrointestinal bleeding during angiography,[12] and pulmonary thromboembolism.[13] Utility of SI has been conflicting in trauma patients[14,15] and not significantly useful in evaluation of critically ill patients with sepsis.[16,17]

Shock index has not been extensively studied in the veterinary literature. In a rat animal model with traumatic brain injury and blood loss, SI had linear correlation with the degree of hemorrhage in the control and the mild brain injury animals but this physiologic response was blunted in the moderate brain injury group. The authors

concluded in the study that SI should be used with caution in animals with traumatic brain injury.[18] Similarly in a pig model of acute hemorrhage, as the degree of hemorrhage increased, SI also increased and an SI > 3 indicated impending cardiovascular collapse. Shock index had an inverse correlation with oxygen delivery.[16] To our knowledge, SI has not been evaluated in clinical veterinary patients. In addition to establishing a normal reference interval for canine shock index, this study compares SI in normal healthy dogs to dogs with known hemorrhage. Our hypothesis is that SI will differentiate a population of dogs with hemorrhagic shock from healthy controls.

Materials and methods

This is a retrospective study using prospectively collected information from two previous studies to compare SI in healthy dogs to dogs with confirmed hemorrhagic shock. The control group (healthy dogs) consists of 78 client, student, and staff owned dogs brought into the small animal clinic that were used to validate the use of a tissue oxygen monitor in dogs.[a] The complete materials and methods have been previously published for this study.[19] Inclusion criteria were body weight > 9 kg, normal physical exam, normal complete blood count (CBC)[b], chemistry profile,[c] and SBP.[d] Blood lactate[e] was also evaluated in these dogs. Heart rate and SBP obtained by certified veterinary technician staff members utilizing standard emergency room equipment [d, f] are used for calculation of SI for the current study.

The hemorrhage group consists of 38 dogs diagnosed with acute hemorrhagic shock that presented to the emergency service. The dogs were enrolled in a study to evaluate the use of a tissue oxygen monitor[a] for identification of shock in dogs compared with

clinician assessment of shock.[20] Hemorrhage was confirmed based on identification of blood within the respective area involved. Hemorrhage dogs had a variety of underlying etiologies including hemorrhaging intra-abdominal mass (n= 20), vehicular trauma (n=5), penetrating trauma (n=3), gastrointestinal hemorrhage (n=3), pericardial effusion (n=2), coagulopathy (n=2), other penetrating injury (n=1), and unknown etiology (n=2). At the time of presentation, patient vitals (temperature and HR) were recorded. Additional data obtained at enrollment included body weight, StO_2,[a] blood lactate,[e] blood pressure,[d, f] CBC,[b] and chemistry profile.[c] Three board certified emergency critical care clinicians blinded to StO_2 results retrospectively classified all patients into one of four levels of shock using the following criteria: Level 1: no shock- patients with no tachycardia, hypotension, normal BE, and minor or insignificant co-morbidities; Level 2: mild shock- patients with mild tachycardia, no hypotension, normal BE, and only minor co-morbidities; Level 3: moderate shock - patients with hypotension, tachycardia responsive to fluid resuscitation, decreased BE, and major co-morbidities. Level 4: severe shock patients-severe hypotension, marked tachycardia, decreased BE, and severe co-morbidities.[21] All patients enrolled in the study were ultimately classified as $\geq$2 by the investigators, consistent with at least mild hemorrhagic shock. Heart rate and SBP obtained at presentation by the emergency room certified veterinary technician staff members utilizing standard emergency room equipment[d, f] are used for calculation of SI for the current study.

Statistical methods

Statistical analysis was performed using a commercially available software program.[g] Data was tested for normality with the Kolmogorov-Smirnov test, and all data were found to be non-normally distributed except body weight and SBP. The Fisher's exact test was used to compare age, temperature, HR, lactate, StO_2, hemoglobin, pH and SI between normal dogs and dogs in the hemorrhage group. Student's t-test was used to compare body weight and SBP between the normal dogs and dogs with hemorrhage. Spearman rank correlation was performed to evaluate for relationships between SI and SBP, HR, body weight, age, temperature, lactate, StO_2, hemoglobin, and pH for all patients and duration of hospitalization for dogs in the hemorrhage group. Logistic regression was used to determine the ability of SI to predict euthanasia or death. A p-value of <0.05 was used to determine statistically significance. Sensitivity and specificity for determining hemorrhagic shock were calculated using 3 SI cut-off points.

Results

Data from each population (healthy controls and hemorrhage) are presented in Table 1. The two groups were similar in weight, but the hemorrhage dogs were significantly older than the healthy control dogs. Shock index was significantly higher in the hemorrhage group than the healthy control group. Hemorrhage dogs had significantly lower body temperatures, SBP, StO_2 and hemoglobin than healthy control dogs. Hemorrhage dogs had significantly higher HR and lactate level than the healthy control dogs. The pH values were not statistically different between groups.

For all dogs, correlations between shock index and measured parameters are reported in Table 2. There was no correlation between SI and weight of the patient. There was a direct linear correlation between SI and age, SI and lactate and shock index and pH. An inverse linear correlation was noted between SI and body temperature, SI and StO_2, and SI and hemoglobin. Because the SI is calculated from the HR and SBP, there is an expected direct and inverse relationship respectively between these measurements and SI. For hemorrhage dogs only, there was no correlation between SI and the length of hospital stay. Based on logistic regression analysis, there was not an increased risk of mortality (death or euthanasia) with increasing SI (OR 0.953, 95% CI 0.418 - 2.172) in dogs with hemorrhage.

Sensitivity and specificity was evaluated for several cut off values of SI (Table 3). For a value of > 0.8 the sensitivity was 0.95 with a specificity of 0.36. If that value is increased to > 0.9, which is a value used in many human studies, the sensitivity decreases slightly to 0.92 with an increase in specificity of 0.5.

Discussion

Shock index is a simple calculation done by dividing the HR by the SBP. This can be done within minutes of a patient's arrival and may provide another triage tool for ER doctors. This study is a retrospective evaluation of patients from two previous study populations and compared the SI between normal healthy dogs and dogs with confirmed hemorrhagic shock. From this study, normal SI for dogs ranges from 0.57 to 1.53 with a median of 0.91. Although some of the hemorrhage dogs had an SI within the normal range, the median values were significantly different between groups and 92% of the

hemorrhage dogs had an SI of > 0.91. When using an SI cut off value of 0.9, there is high sensitivity but low specificity as a triage tool. Therefore, if the SI is > 0.9, further evaluation for hemorrhage should be performed. Similar to other triage tools or scoring systems, SI should be used in addition to clinical evaluation rather than a definitive tool for creating treatment and diagnostic plans or determining prognosis for patients.

Median heart rates and blood pressures were significantly different between the control and hemorrhage dogs. Despite this, the median values for systolic blood pressure in both populations were within the normal reference interval for dogs. Normal SBP is a typical physiologic response in early hemorrhage until greater than 15 to 30% of blood volume is lost. Due to individual patient variation, mild changes in heart rate and systolic blood pressure values in early compensatory shock may be altered from the patient's baseline, yet remain in the normal reference interval for the population of a given species. By creating a ratio of the two values, SI compares the changes in heart rate and blood pressure together in an attempt to identify subtle changes in both parameters and detect early hypovolemia.[22] While the data in this study do not justify shock index as a superior tool to SBP or HR, the data support its ability to differentiate a normal population from a hemorrhagic shock population. Further prospective evaluation of its application as a triage tool in comparison to other presenting triage variables in patient's in shock is currently underway.

There was a direct correlation of SI with age when evaluating the whole population of dogs. This correlation is likely due to an older population of dogs in hemorrhagic shock, rather than a direct cause and effect related to age and shock index.

Although not evaluated in our study, older dogs may have concurrent disease processes that can contribute to HR and SBP abnormalities including primary cardiovascular disease, renal disease, Cushing's disease, and thyroid disease, which may affect SI. Aged matched controls for future studies would be needed to attempt to rule out confounding factors associated with aging. In one human study, this has been addressed by including the patient's age in elderly patients when calculating the SI.[5] This was not done in our study but can be considered in future studies to determine if this additional calculation is necessary in geriatric veterinary patients. Our study did not include a significant number of puppies and values for very young dogs, especially those in shock, may be significantly different from adult dogs. Further investigation in neonates and puppies should be evaluated to determine a normal SI for these populations.

Both patient populations were similar in body weight and there was no correlation between SI and weight. The mean body weights for the populations were 27.1 kg and 26.3 kg, which would be considered medium to large breed dogs. The SI values of our study may not be representative of giant and toy breed dogs and further study in these patient populations may be warranted to establish normal values.

An unexpected finding in this study was that the SI had linear correlation with the pH. This correlation looked at the population of dogs as a whole and both groups had median pH values within normal reference range. With multiple contributing factors to pH (ie. respiratory, metabolic, strong ions, etc.), we were unable to elucidate the cause of this correlation but it is unlikely to be a clinically relevant finding from this study.

Blood pressure technique should be considered when evaluating SI. Blood pressure measurements were all indirect in this study but were not standardized with both Doppler and oscillometric used in the hemorrhage population. Blood pressures were performed in the emergency room and although the technique is typically done according to recommended blood pressure measurement guidelines, blood pressure measurements were not standardized to a specific limb or cuff size measurement in the hemorrhage study.[23] Doppler blood pressure measurement is often used in smaller or unstable patients and the blood pressure value obtained in dogs has been more closely correlated to SBP so this technique may be preferred.[24] Additionally, no indirect blood pressure monitoring device is validated for use in veterinary patients and there have been conflicting results when comparing indirect devices to other indirect devices as well as to direct arterial blood pressure measurement.[25-29] Although direct measurements are impractical in the emergency room setting, this technique could be used in ICU, during anesthesia, or in post-operative patients to calculate SI and evaluate for acute blood loss. A prospective study comparing direct arterial, Doppler, and oscillometric devices could be performed to evaluate the use of these devices compared to the gold standard in calculating SI. If monitoring trends in SI, the same technique should be used so that the value is consistent between measurements.

Because the data was evaluated retrospectively, there are limitations to the study. The healthy control dogs were younger than the hemorrhage population. Ideally there should be age matched controls to decrease the effect that age and potential co-morbidities may have on the HR and blood pressure. As previously discussed, this may

be addressed by incorporating the patient's age into the calculation and can be considered in future studies to determine if this is necessary in veterinary patients. Control dogs were studied in a different room within the hospital and not in the emergency room. Despite this, these dogs were still in a hospital setting, in a room off a busy hallway in the hospital, had blood drawn, blood pressure evaluation and tissue oxygenation measurements done, which for some dogs was very stressful per the author of that study. Although the environment (a quiet room versus busy ER, with or without the owner) needs to be taken into consideration when evaluating patients to account for the effect on heart rate and blood pressure values, both populations were evaluated within the hospital and therefore the study location should not be a significant factor in our study.[23]

The lactate analyzer used in the study has not been validated for use in dogs but is a common instrument used in veterinary clinics. In one study evaluating its use in dogs, it had good precision for use but did not correlate with another method for lactate measurement.[30] Because of this, as with other blood work, lactate values should only be compared if using the same instrument. Finally, our study only evaluated normal dogs and dogs with hemorrhage. Further investigation is needed in other populations of sick patients.

Conclusions:

Despite the limitations of the study, shock index is a simple and easy calculation that can be used in the emergency setting. Although there is some overlap of SI between normal dogs and the hemorrhage population, the calculation can be used as an additional triage tool for emergency doctors and may prompt further investigation for hemorrhage if

the value is above 0.9. Additionally, SI may be valuable as enrollment criteria for clinical studies, as a baseline characteristic for clinical trial arms to assess appropriate randomization, and for evaluating response to interventions in hemorrhagic shock patients.

Footnotes:

a. InSpectra Tissue Spectrometer, Hutchinson Technology Inc, BioMeasurement Division, Hutchinson, MN.

b. Cell-Dyn 3500, Abbott, Chicago, IL.

c. Olympus AU400, Olympus America Inc, Center Valley, PA.

d. Parks Medical Model #811B, Parks Medical, Aloha, OR.

e. Accutrend lacate, Sports resource group, Hawthorne, NY

f. BCI Advisor, Smiths Group, London, England.

g. SAS version 9.2, SAS Institute, Inc., Cary, NC.

Table 1. Comparison of parameters between hemorrhagic shock (n=38) and healthy control dogs (n=78).

Parameter	Hemorrhagic shock	Healthy	p-value
Body weight* (kg)	27.1 (11.7)	26.3 (9.8)	0.7
Age (years)	8.5 (0.58 – 13.58)	4.3 (1.4-8.5)	<**0.001**
Temperature (^{0} C)	38.7 (35.6- 39.9)	38.7 (37.5 - 39.9)	<**0.001**
Heart rate (bpm)	150 (120 – 220)	110 (80 – 150)	<**0.001**
SBP* (mmHg)	112.2 (35.8)	124.6 (21.5)	<**0.02**
Lactate (mmol/L)	0.51 (0.078 - 1.41)	0.11 (0.033 to 0.33)	<**0.001**
StO2 (%)	84 (23 – 94)	94 (56 – 99)	<**0.001**
Hemoglobin (g/L)	81 (56 – 183)	162.5 (133 – 198)	<**0.001**
pH	7.401 (6.962 – 7.485)	7.382 (7.310 – 7.459)	0.15
SI	1.37 (0.78 – 4.35)	0.91 (0.57 – 1.53)	<**0.001**

*Normally distributed data: reported as mean (standard deviation), other data reported as median (range).

Table 2. Correlation between SI and evaluated parameters in all dogs (n=116).

Parameter	R^2	p-value
Body weight	0.01	0.29
Age	0.044	**0.026**
Temperature	0.07	**0.0046**
Heart rate	0.48	**<0.001**
Systolic blood pressure	0.51	**<0.001**
Lactate	0.39	**<0.001**
StO2	0.077	**0.003**
Hemoglobin	0.21	**<0.001**
pH	0.037	**0.04**
Duration of hospitalization (hemorrhage only)	0.033	0.274

Table 3: Sensitivity and specificity for SI at 3 cut points

Shock index	Sensitivity	Specificity
>0.8	0.95	0.36
>0.9	0.92	0.50
>1.0	0.79	0.69

Bibliography:

References Introduction:

1. Khanna C, London C, Vail D, Mazcko C, Hirschfeld S. Guiding the optimal translation of new cancer treatments from canine to human cancer patients. Clin Cancer Res 2009 Sep 15;15(18):5671-5677.

2. Leppik IE, Patterson EN, Coles LD, Craft EM, Cloyd JC. Canine status epilepticus: a translational platform for human therapeutic trials. Epilepsia 2011 Oct;52 Suppl 8:31-34.

3. Ostrander EA. Franklin H. Epstein Lecture. Both ends of the leash--the human links to good dogs with bad genes. N Engl J Med 2012 Aug 16;367(7):636-646.

a. InSpectra Tissue Spectrometer, Hutchinson Technology Inc, BioMeasurement Division, Hutchinson, MN.

References Project #1:

(1) Muir W. Trauma: physiology, pathophysiology, and clinical implications. Journal of Veterinary Emergency & Critical Care 2006 12;16(4):253-263.

(2) Minino AM, Heron MP, Smith BL. Deaths: Preliminary Data for 2004. National Vital Statistics Reports 2006;54(19):1-50.

(3) Simpson SA, Syring R, Otto CM. Severe blunt trauma in dogs: 235 cases (1997-2003). J Vet Emerg Crit Care (San Antonio) 2009 Dec;19(6):588-602.

(4) Kolata RJ, Johnston DE. Motor vehicle accidents in urban dogs: a study of 600 cases. J Am Vet Med Assoc 1975 Nov 15;167(10):938-941.

(5) Minino AM, Anderson RN, Fingerhut LA, Boudreault MA, Warner M. Deaths: Injuries, 2002. National Vital Statistics Reports 2006;54(10):1-128.

(6) Highlights From Injury Facts. Available at: http://www.nsc.org/news_resources/injury_and_death_statistics/Pages/HighlightsFromInjuryFacts.aspx. Accessed 5/9/2010, 2010.

(7) Pfeifer R, Tarkin IS, Rocos B, Pape HC. Patterns of mortality and causes of death in polytrauma patients--has anything changed? Injury 2009 Sep;40(9):907-911.

(8) Dewar D, Moore FA, Moore EE, Balogh Z. Postinjury multiple organ failure. Injury 2009 Sep;40(9):912-918.

(9) Giannoudis PV, Stengel D. Clinical research in trauma and orthopaedic surgery--call for action. Injury 2008 Jun;39(6):627-630.

(10) Keramaris NC, Kanakaris NK, Tzioupis C, Kontakis G, Giannoudis PV. Translational research: from benchside to bedside. Injury 2008 Jun;39(6):643-650.

(11) Nomellini V, Gomez CR, Gamelli RL, Kovacs EJ. Aging and animal models of systemic insult: trauma, burn, and sepsis. Shock 2009 Jan;31(1):11-20.

(12) McIntosh TK, Vink R, Noble L, Yamakami I, Fernyak S, Soares H, et al. Traumatic brain injury in the rat: characterization of a lateral fluid-percussion model. Neuroscience 1989;28(1):233-244.

(13) Kobbe P, Vodovotz Y, Kaczorowski DJ, Mollen KP, Billiar TR, Pape HC. Patterns of cytokine release and evolution of remote organ dysfunction after bilateral femur fracture. Shock 2008 Jul;30(1):43-47.

(14) Hauser CJ. Preclinical models of traumatic, hemorrhagic shock. Shock 2005 Dec;24 Suppl 1:24-32.

(15) Flohe SB, Flohe S, Schade FU. Invited review: deterioration of the immune system after trauma: signals and cellular mechanisms. Innate Immun 2008 Dec;14(6):333-344.

(16) Singh G, Chaudry KI, Chudler LC, Chaudry IH. Depressed gut absorptive capacity early after trauma-hemorrhagic shock. Restoration with diltiazem treatment. Ann Surg 1991 Dec;214(6):712-718.

(17) Wang P, Ba ZF, Burkhardt J, Chaudry IH. Trauma-hemorrhage and resuscitation in the mouse: effects on cardiac output and organ blood flow. Am J Physiol 1993 Apr;264(4 Pt 2):H1166-73.

(18) Zellweger R, Ayala A, Zhu XL, Morrison MH, Chaudry IH. Effect of surgical trauma on splenocyte and peritoneal macrophage immune function. J Trauma 1995 Oct;39(4):645-650.

(19) Wichmann MW, Ayala A, Chaudry IH. Severe depression of host immune functions following closed-bone fracture, soft-tissue trauma, and hemorrhagic shock. Crit Care Med 1998 Aug;26(8):1372-1378.

(20) Kolata RJ, Kraut NH, Johnston DE. Patterns of trauma in urban dogs and cats: a study of 1,000 cases. J Am Vet Med Assoc 1974 Mar 1;164(5):499-502.

(21) Hayes G, Mathews K, Doig G, Kruth S, Boston S, Nykamp S, et al. The acute patient physiologic and laboratory evaluation (APPLE) score: a severity of illness stratification system for hospitalized dogs. J Vet Intern Med 2010 Sep-Oct;24(5):1034-1047.

(22) Hall KE, Holowaychuk MK, Sharp CR, Reineke E. A multi-center eight-week prospective cohort study of 301 dogs sustaining trauma. Proceedings of the 18th

International Veterinary Emergency and Critical Care Symposium; 2012 Sep 8-12; San Antonio, Texas.

(23) Fleming JM, Creevy KE, Promislow DE. Mortality in north american dogs from 1984 to 2004: an investigation into age-, size-, and breed-related causes of death. J Vet Intern Med 2011 Mar-Apr;25(2):187-198.

(24) Powell LL, Rozanski EA, Tidwell AS, Rush JE. A Retrospective Analysis of Pulmonary Contusion Secondary to Motor Vehicular Accidents in 143 Dogs: 1994-1997. Journal of Veterinary Emergency and Critical Care 1999;9:127-136.

(25) Streeter EM, Rozanski EA, Laforcade-Buress A, Freeman LM, Rush JE. Evaluation of vehicular trauma in dogs: 239 cases (January-December 2001). J Am Vet Med Assoc 2009 Aug 15;235(4):405-408.

(26) Choudhry MA, Bland KI, Chaudry IH. Trauma and immune response--effect of gender differences. Injury 2007 Dec;38(12):1382-1391.

(27) Trupka A, Waydhas C, Hallfeldt KK, Nast-Kolb D, Pfeifer KJ, Schweiberer L. Value of thoracic computed tomography in the first assessment of severely injured patients with blunt chest trauma: results of a prospective study. J Trauma 1997 Sep;43(3):405-11; discussion 411-2.

(28) American College of Surgeons - National Trauma Data Bank (NTDB). Available at: http://www.facs.org/trauma/ntdb/docpub.html. Accessed December 19, 2011.

(29) Sigrist NE, Doherr MG, Spreng DE. Clinical findings and diagnostic value of post-traumatic thoracic radiographs in dogs and cats with blunt trauma. Journal of Veterinary Emergency and Critical Care 2004;14(4):259-268.

(30) Tamas P, Paddleford R, Krahwinkel Jr D. Thoracic trauma in dogs and cats presented for limb fractures. The Journal of the American Animal Hospital Association (USA) 1985.

(31) Lisciandro GR, Lagutchik MS, Mann KA, Voges AK, Fosgate GT, Tiller EG, et al. Evaluation of a thoracic focused assessment with sonography for trauma (TFAST) protocol to detect pneumothorax and concurrent thoracic injury in 145 traumatized dogs. Journal of Veterinary Emergency & Critical Care 2008 06;18(3):258-269.

(32) Boysen SR, Rozanski EA, Tidwell AS, Holm JL, Shaw SP, Rush JE. Evaluation of a focused assessment with sonography for trauma protocol to detect free abdominal fluid in dogs involved in motor vehicle accidents. J Am Vet Med Assoc 2004 Oct 15;225(8):1198-1204.

(33) Olsen D, Renberg W, Perrett J, Hauptman JG, Waldron DR, Monnet E. Clinical management of flail chest in dogs and cats: a retrospective study of 24 cases (1989-1999). J Am Anim Hosp Assoc 2002 Jul-Aug;38(4):315-320.

(34) Spackman CJ, Caywood DD, Feeney DA, Johnston GR. Thoracic wall and pulmonary trauma in dogs sustaining fractures as a result of motor vehicle accidents. J Am Vet Med Assoc 1984 Nov 1;185(9):975-977.

(35) Moore CL, Copel JA. Point-of-care ultrasonography. N Engl J Med 2011 Feb 24;364(8):749-757.

(36) Lisciandro GR. Abdominal and thoracic focused assessment with sonography for trauma, triage, and monitoring in small animals. J Vet Emerg Crit Care (San Antonio) 2011 Apr;21(2):104-122.

(37) Lisciandro GR, Lagutchik MS, Mann KA, Fosgate GT, Tiller EG, Cabano NR, et al. Evaluation of an abdominal fluid scoring system determined using abdominal focused assessment with sonography for trauma in 101 dogs with motor vehicle trauma. J Vet Emerg Crit Care (San Antonio) 2009 Oct;19(5):426-437.

(38) Giannoudis PV, Giannoudi M, Stavlas P. Damage control orthopaedics: lessons learned. Injury 2009 Nov;40 Suppl 4:S47-52.

(39) Pang JM, Civil I, Ng A, Adams D, Koelmeyer T. Is the trimodal pattern of death after trauma a dated concept in the 21st century? Trauma deaths in Auckland 2004. Injury 2008 Jan;39(1):102-106.

(40) Baker CC, Oppenheimer L, Stephens B, Lewis FR, Trunkey DD. Epidemiology of trauma deaths. Am J Surg 1980 Jul;140(1):144-150.

(41) Chiara O, Scott JD, Cimbanassi S, Marini A, Zoia R, Rodriguez A, et al. Trauma deaths in an Italian urban area: an audit of pre-hospital and in-hospital trauma care. Injury 2002 Sep;33(7):553-562.

(42) Meislin H, Criss EA, Judkins D, Berger R, Conroy C, Parks B, et al. Fatal trauma: the modal distribution of time to death is a function of patient demographics and regional resources. J Trauma 1997 Sep;43(3):433-440.

(43) Salim A, Hadjizacharia P, Dubose J, Brown C, Inaba K, Chan LS, et al. Persistent hyperglycemia in severe traumatic brain injury: an independent predictor of outcome. Am Surg 2009 Jan;75(1):25-29.

(44) Syring RS, Otto CM, Drobatz KJ. Hyperglycemia in dogs and cats with head trauma: 122 cases (1997-1999). J Am Vet Med Assoc 2001 Apr 1;218(7):1124-1129.

(45) Platt SR, Radaelli ST, McDonnell JJ. Computed tomography after mild head trauma in dogs. Vet Rec 2002 Aug 24;151(8):243.

(46) Platt SR, Radaelli ST, McDonnell JJ. The prognostic value of the modified Glasgow Coma Scale in head trauma in dogs. J Vet Intern Med 2001 Nov-Dec;15(6):581-584.

(47) Kitagawa M, Okada M, Kanayama K, Sakai T. Traumatic intracerebral hematoma in a dog: MR images and clinical findings. J Vet Med Sci 2005 Aug;67(8):843-846.

(48) Cabassu JB, Cabassu JP, Brochier L, Catheland S, Ivanoff S. Surgical treatment of a traumatic intracranial epidural haematoma in a dog. Vet Comp Orthop Traumatol 2008;21(5):457-461.

(49) Foley C, Bracker K, Drellich S. Hypothalamic-pituitary axis deficiency following traumatic brain injury in a dog. J Vet Emerg Crit Care (San Antonio) 2009 Jun;19(3):269-274.

(50) Hayes GM. Severe seizures associated with traumatic brain injury managed by controlled hypothermia, pharmacologic coma, and mechanical ventilation in a dog. J Vet Emerg Crit Care (San Antonio) 2009 Dec;19(6):629-634.

(51) Brun-Buisson C. The epidemiology of the systemic inflammatory response. Intensive Care Med 2000;26 Suppl 1:S64-74.

(52) Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. JAMA 1995 Jan 11;273(2):117-123.

(53) Roumen RM, Hendriks T, van der Ven-Jongekrijg J, Nieuwenhuijzen GA, Sauerwein RW, van der Meer JW, et al. Cytokine patterns in patients after major vascular

surgery, hemorrhagic shock, and severe blunt trauma. Relation with subsequent adult respiratory distress syndrome and multiple organ failure. Ann Surg 1993 Dec;218(6):769-776.

(54) Sharp CR, Chang CH, DeClue AE. Inflammatory biomarkers for canine sepsis. American College of Veterinary Internal Medicine Focum 2010.

(55) Trunkey DD, Shires GT, Mc Clelland R. Management of liver trauma in 811 consecutive patients. Ann Surg 1974 May;179(5):722-728.

(56) Keel M, Trentz O. Pathophysiology of polytrauma. Injury 2005 Jun;36(6):691-709.

(57) Schroeder JE, Weiss YG, Mosheiff R. The current state in the evaluation and treatment of ARdS and SIRS. Injury 2009 Nov;40 Suppl 4:S82-9.

(58) Yendamuri S, Fulda GJ, Tinkoff GH. Admission hyperglycemia as a prognostic indicator in trauma. J Trauma 2003 Jul;55(1):33-38.

(59) Johnston CJ, Rubenfeld GD, Hudson LD. Effect of age on the development of ARDS in trauma patients. Chest 2003 Aug;124(2):653-659.

(60) Campbell VL, King LG. Pulmonary function, ventilator management, and outcome of dogs with thoracic trauma and pulmonary contusions: 10 cases (1994-1998). J Am Vet Med Assoc 2000 Nov 15;217(10):1505-1509.

(61) Maegele M, Lefering R, Yucel N, Tjardes T, Rixen D, Paffrath T, et al. Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients. Injury 2007 Mar;38(3):298-304.

(62) Holmes JF, Goodwin HC, Land C, Kuppermann N. Coagulation testing in pediatric blunt trauma patients. Pediatr Emerg Care 2001 Oct;17(5):324-328.

(63) Meissner MH, Chandler WL, Elliott JS. Venous thromboembolism in trauma: a local manifestation of systemic hypercoagulability? J Trauma 2003 Feb;54(2):224-231.

(64) Parr MJ, Bouillon B, Brohi K, Dutton RP, Hauser CJ, Hess JR, et al. Traumatic coagulopathy: where are the good experimental models? J Trauma 2008 Oct;65(4):766-771.

(65) Otto CM. Clinical trials in spontaneous disease in dogs: a new paradigm for investigations of sepsis. Journal of Veterinary Emergency and Critical Care 2007;17(4):359-367.

(66) Otto CM, Rieser TM, Brooks MB, Russell MW. Evidence of hypercoagulability in dogs with parvoviral enteritis. J Am Vet Med Assoc 2000 Nov 15;217(10):1500-1504.

(67) de Laforcade AM, Rozanski EA, Freeman LM, Li W. Serial evaluation of protein C and antithrombin in dogs with sepsis. J Vet Intern Med 2008 Jan-Feb;22(1):26-30.

(68) de Laforcade AM, Freeman LM, Shaw SP, Brooks MB, Rozanski EA, Rush JE. Hemostatic changes in dogs with naturally occurring sepsis. J Vet Intern Med 2003 Sep-Oct;17(5):674-679.

(69) Kenney EM, Rozanski EA, Rush JE, deLaforcade-Buress AM, Berg JR, Silverstein DC, et al. Association between outcome and organ system dysfunction in dogs with sepsis: 114 cases (2003-2007). J Am Vet Med Assoc 2010 Jan 1;236(1):83-87.

(70) Kuzi S, Segev G, Haruvi E, Aroch I. Plasma Antithrombin Activity as a Diagnostic and Prognostic Indicator in Dogs: A Retrospective Study of 149 Dogs. J Vet Intern Med 2010 Apr 2.

(71) Wagg CR, Boysen SR, Bedard C. Thrombelastography in dogs admitted to an intensive care unit. Vet Clin Pathol 2009 Jun 22.

(72) Hess JR, Brohi K, Dutton RP, Hauser CJ, Holcomb JB, Kluger Y, et al. The coagulopathy of trauma: a review of mechanisms. J Trauma 2008 Oct;65(4):748-754.

(73) Stahel PF, Smith WR, Moore EE. Current trends in resuscitation strategy for the multiply injured patient. Injury 2009 Nov;40 Suppl 4:S27-35.

(74) Bartal C, Yitzhak A. The role of thromboelastometry and recombinant factor VIIa in trauma. Curr Opin Anaesthesiol 2009 Apr;22(2):281-288.

(75) Abstracts from the International Veterinary Emergency and Critical Care Symposium and the European Veterinary Emergency and Critical Care Society Annual Congress, 2011. Journal of Veterinary Emergency and Critical Care 2011;21(s1):S1-S26.

(76) Osler T, Baker SP, Long W. A modification of the injury severity score that both improves accuracy and simplifies scoring. J Trauma 1997 Dec;43(6):922-5; discussion 925-6.

(77) Rockar RA, Drobatz KS, Shofer FS. Development of a scoring system for the veterinary trauma patient. Journal of Veterinary Emergency & Critical Care 1994;4(2):77-84.

(78) Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 4;42(2):377-381.

(79) Khanna C, London C, Vail D, Mazcko C, Hirschfeld S. Guiding the optimal translation of new cancer treatments from canine to human cancer patients. Clin Cancer Res 2009 Sep 15;15(18):5671-5677.

(80) Leppik IE, Patterson EN, Coles LD, Craft EM, Cloyd JC. Canine status epilepticus: a translational platform for human therapeutic trials. Epilepsia 2011 Oct;52 Suppl 8:31-34.

(81) Ostrander EA. Franklin H. Epstein Lecture. Both ends of the leash--the human links to good dogs with bad genes. N Engl J Med 2012 Aug 16;367(7):636-646.

References Project #2:

1. Muir W. Trauma: Physiology, pathophysiology, and clinical implications. *Journal of Veterinary Emergency & Critical Care*. 2006;16(4):253-263.

2. Kolata RJ, Kraut NH, Johnston DE. Patterns of trauma in urban dogs and cats: A study of 1,000 cases. *J Am Vet Med Assoc*. 1974;164(5):499-502.

3. Hayes G, Mathews K, Doig G, et al. The acute patient physiologic and laboratory evaluation (APPLE) score: A severity of illness stratification system for hospitalized dogs. *J Vet Intern Med*. 2010;24(5):1034-1047. doi: 10.1111/j.1939-1676.2010.0552.x; 10.1111/j.1939-1676.2010.0552.x.

4. Fleming JM, Creevy KE, Promislow DE. Mortality in north american dogs from 1984 to 2004: An investigation into age-, size-, and breed-related causes of death. *J Vet Intern*

Med. 2011;25(2):187-198. doi: 10.1111/j.1939-1676.2011.0695.x; 10.1111/j.1939-1676.2011.0695.x.

5. Simpson SA, Syring R, Otto CM. Severe blunt trauma in dogs: 235 cases (1997-2003). *J Vet Emerg Crit Care (San Antonio)*. 2009;19(6):588-602.

6. Streeter EM, Rozanski EA, Laforcade-Buress A, Freeman LM, Rush JE. Evaluation of vehicular trauma in dogs: 239 cases (january-december 2001). *J Am Vet Med Assoc*. 2009;235(4):405-408.

7. Powell LL, Rozanski EA, Tidwell AS, Rush JE. A retrospective analysis of pulmonary contusion secondary to motor vehicular accidents in 143 dogs: 1994-1997. *Journal of Veterinary Emergency and Critical Care*. 1999;9:127-136.

8. Kolata RJ, Johnston DE. Motor vehicle accidents in urban dogs: A study of 600 cases. *J Am Vet Med Assoc*. 1975;167(10):938-941.

9. Hayes G, Mathews K, Kruth S, Doig G, Dewey C. Illness severity scores in veterinary medicine: What can we learn? *Journal of Veterinary Internal Medicine*. 2010;24(3):457-466. doi: 10.1111/j.1939-1676.2010.0483.x.

10. Rockar RA, Drobatz KS, Shofer FS. Development of a scoring system for the veterinary trauma patient. *Journal of Veterinary Emergency & Critical Care*. 1994;4(2):77-84.

11. Holowaychuk MK, Monteith G. Ionized hypocalcemia as a prognostic indicator in dogs following trauma. *J Vet Emerg Crit Care (San Antonio)*. 2011;21(5):521-530. doi: 10.1111/j.1476-4431.2011.00675.x; 10.1111/j.1476-4431.2011.00675.x.

12. Platt SR, Radaelli ST, McDonnell JJ. The prognostic value of the modified glasgow coma scale in head trauma in dogs. *J Vet Intern Med*. 2001;15(6):581-584.

13. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381. doi: 10.1016/j.jbi.2008.08.010.

14. Hosgood G, Scholl D. Evalution of age as a risk factor for perianesthetic morbidity and mortality in the dog. *Journal of Veterinary Emergency and Critical Care*. 1998;8(3):222-236. doi: 10.1111/j.1476-4431.1998.tb00128.x.

15. Lisciandro GR, Lagutchik MS, Mann KA, et al. Evaluation of an abdominal fluid scoring system determined using abdominal focused assessment with sonography for trauma in 101 dogs with motor vehicle trauma. *J Vet Emerg Crit Care (San Antonio)*. 2009;19(5):426-437.

16. Pang DS, Boysen S. Lactate in veterinary critical care: Pathophysiology and management. *J Am Anim Hosp Assoc*. 2007;43(5):270-279.

17. Fullington RJ, Otto CM. Characteristics and management of gunshot wounds in dogs and cats: 84 cases (1986-1995). *J Am Vet Med Assoc*. 1997;210(5):658-662.

18. McGwin G,Jr, Nunn AM, Mann JC, et al. Reassessment of the tri-modal mortality distribution in the presence of a regional trauma system. *J Trauma*. 2009;66(2):526-530. doi: 10.1097/TA.0b013e3181623321.

References Project #3:

1. www.htibiomeasurement.com

2. Crookes BA, Cohn SM, et al. Can Near-Infrared Spectroscopy Identify the Severity of Shock in Trauma Patients? *J Trauma*. 2005;58:806-816.

3. Taylor JH, Mulier KE, Myers DE, Beilman GJ. Use of Near-Infrared Spectroscopy in Early Determination of Irreversible Hemorrhagic Shock. *J Trauma* 2005;58:1119-1125.

4. Crookes BA, Cohn SM, Burton EA, Nelson J, Proctor KG. Noninvasive muscle oxygenation to guide fluid resuscitation after traumatic shock. *Surgery*. 2004;135:662-670.

5. Rivers E, Nguyen B, Havstad S, et al. Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock. *N Engl J Med*. 2001; 345(19):1368.

6. Smith J, Bricker S, Putnam B. Tissue oxygen saturation predicts the need for early blood transfusion in trauma patients *Am Surg*. 2008;74(10):1006-1011

7. Hall, Kelly E., Powell L.L., et al. Measurement of tissue oxygen saturation levels using portable near-infrared spectroscopy in clinically healthy dogs. *J Vet Emerg Crit Care*. 2008:18(6):594-600.

8. Prittie, J. Optimal endpoints of resuscitation and early goal-directed therapy. *J Vet Emerg Crit Care*. 2006; 16(4):329-339.

9. Cohn S, Nathens A, Moore FA, et al. Tissue oxygen saturation predicts the development of organ dysfunction during traumatic shock resuscitation. *J Trauma* 2007:62:44-55.

10. Beilman GJ, Groehler KE, et al. Near-Infrared spectroscopy measurement of regional tissue oxyhemoglobin saturation during hemorrhagic shock. *Shock* 1999:12:196-200.

11. Lipcsey M, Eastwood GM, Woinarski NC, Bellomo R. Near-infrared spectroscopy of the thenar eminence: comparison of dynamic testing protocols. *Crit Care Resusc.* 2012 Jun;14(2):142-7.

References Project #4:

1. Birkhahn RH, Gaeta TJ, Terry D, Bove JJ, Tloczkowski J. Shock index in diagnosing early acute hypovolemia. *Am J Emerg Med*. 2005;23(3):323-326.

2. Cannon CM, Braxton CC, Kling-Smith M, Mahnken JD, Carlton E, Moncure M. Utility of the shock index in predicting mortality in traumatically injured patients. *J Trauma*. 2009;67(6):1426-1430. doi: 10.1097/TA.0b013e3181bbf728.

3. Vandromme MJ, Griffin RL, Kerby JD, McGwin G,Jr, Rue LW,3rd, Weinberg JA. Identifying risk for massive transfusion in the relatively normotensive patient: Utility of the prehospital shock index. *J Trauma*. 2011;70(2):384-8; discussion 388-90. doi: 10.1097/TA.0b013e3182095a0a.

4. Bilkova D, Motovska Z, Widimsky P, Dvorak J, Lisa L, Budesinsky T. Shock index: A simple clinical parameter for quick mortality risk assessment in acute myocardial infarction. *Can J Cardiol*. 2011. doi: 10.1016/j.cjca.2011.07.008.

5. Zarzaur BL, Croce MA, Fischer PE, Magnotti LJ, Fabian TC. New vitals after injury: Shock index for the young and age x shock index for the old. *J Surg Res*. 2008;147(2):229-236. doi: 10.1016/j.jss.2008.03.025.

6. Birkhahn RH, Gaeta TJ, Van Deusen SK, Tloczkowski J. The ability of traditional vital signs and shock index to identify ruptured ectopic pregnancy. *Obstet Gynecol*. 2003;189(5):1293-1296. doi: 10.1067/S0002-9378(03)00663-X.

7. Kahyaoglu S, Turgay I, Gocmen M, Sut N, Batioglu S. A new predictive scoring system including shock index for unruptured tubal pregnancy patients. *Eur J Obstet Gynecol Reprod Biol*. 2006;126(1):99-103. doi: 10.1016/j.ejogrb.2005.09.006.

8. Keller AS, Kirkland LL, Rajasekaran SY, Cha S, Rady MY, Huddleston JM. Unplanned transfers to the intensive care unit: The role of the shock index. *J Hosp Med*. 2010;5(8):460-465. doi: 10.1002/jhm.779.

9. Myint PK, Bhaniani A, Bradshaw SM, Alobeidi F, Tariq SM. Usefulness of shock index and adjusted shock index in the severity assessment of community-acquired pneumonia. *Respiration*. 2009;77(4):468-469. doi: 10.1159/000205821.

10. Sankaran P, Kamath AV, Tariq SM, et al. Are shock index and adjusted shock index useful in predicting mortality and length of stay in community-acquired pneumonia? *Eur J Intern Med*. 2011;22(3):282-285. doi: 10.1016/j.ejim.2010.12.009.

11. Myint PK, Musonda P, Sankaran P, et al. Confusion, urea, respiratory rate and shock index or adjusted shock index (CURSI or CURASI) criteria predict mortality in community-acquired pneumonia. *Eur J Intern Med*. 2010;21(5):429-433. doi: 10.1016/j.ejim.2010.07.005.

12. Nakasone Y, Ikeda O, Yamashita Y, Kudoh K, Shigematsu Y, Harada K. Shock index correlates with extravasation on angiographs of gastrointestinal hemorrhage: A logistics regression analysis. *Cardiovasc Intervent Radiol*. 2007;30(5):861-865. doi: 10.1007/s00270-007-9131-5.

13. Toosi MS, Merlino JD, Leeper KV. Prognostic value of the shock index along with transthoracic echocardiography in risk stratification of patients with acute pulmonary embolism. *Am J Cardiol*. 2008;101(5):700-705. doi: 10.1016/j.amjcard.2007.10.038.

14. Convertino VA, Ryan KL, Rickards CA, et al. Physiological and medical monitoring for en route care of combat casualties. *J Trauma*. 2008;64(4 Suppl):S342-53. doi: 10.1097/TA.0b013e31816c82f4.

15. Paladino L, Subramanian RA, Nabors S, Sinert R. The utility of shock index in differentiating major from minor injury. *Eur J Emerg Med*. 2011;18(2):94-98. doi: 10.1097/MEJ.0b013e32833f212b.

16. Rady MY, Nightingale P, Little RA, Edwards JD. Shock index: A re-evaluation in acute circulatory failure. *Resuscitation*. 1992;23(3):227-234.

17. Rady MY, Rivers EP, Nowak RM. Resuscitation of the critically ill in the ED: Responses of blood pressure, heart rate, shock index, central venous oxygen saturation, and lactate. *Am J Emerg Med*. 1996;14(2):218-225.

18. McMahon CG, Kenny R, Bennett K, Little R, Kirkman E. The effect of acute traumatic brain injury on the performance of shock index. *J Trauma*. 2010;69(5):1169-1175. doi: 10.1097/TA.0b013e3181cc8889.

19. Hall K,E., Powell L,L., Beilman G,J., Shafer K,R., Skala V,K., Olmstead E,A. Measurement of tissue oxygen saturation levels using portable near-infrared spectroscopy in clinically healthy dogs. .

20. Gray S, Hall K, Powell L, Schildt J, Brearley A. TISSUE OXYGEN SATURATION IN DOGS PRESENTING FOR ACUTE HEMORRHAGE. *Journal of veterinary emergency and critical care (San Antonio, Tex.: 2001)*. 2011;21(s1):S5.

21. Crookes BA, Cohn SM, Bloch S, et al. Can near-infrared spectroscopy identify the severity of shock in trauma patients? *J Trauma*. 2005;58(4):806-13; discussion 813-6.

22. Gutierrez G, Reines HD, Wulf-Gutierrez ME. Clinical review: Hemorrhagic shock. *Crit Care*. 2004;8(5):373-381. doi: 10.1186/cc2851.

23. Brown S, Atkins C, Bagley R, et al. Guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats. *J Vet Intern Med*. 2007;21(3):542-558.

24. Haberman CE, Kang CW, Morgan JD, Brown SA. Evaluation of oscillometric and doppler ultrasonic methods of indirect blood pressure estimation in conscious dogs. *Can J Vet Res*. 2006;70(3):211-217.

25. Bosiack AP, Mann FA, Dodam JR, Wagner-Mann CC, Branson KR. Comparison of ultrasonic doppler flow monitor, oscillometric, and direct arterial blood pressure measurements in ill dogs. *J Vet Emerg Crit Care (San Antonio)*. 2010;20(2):207-215. doi: 10.1111/j.1476-4431.2010.00520.x.

26. Wernick MB, Hopfner RM, Francey T, Howard J. Comparison of arterial blood pressure measurements and hypertension scores obtained by use of three indirect measurement devices in hospitalized dogs. *J Am Vet Med Assoc*. 2012;240(8):962-968. doi: 10.2460/javma.240.8.962.

27. Chetboul V, Tissier R, Gouni V, et al. Comparison of doppler ultrasonography and high-definition oscillometry for blood pressure measurements in healthy awake dogs. *Am J Vet Res*. 2010;71(7):766-772. doi: 10.2460/ajvr.71.7.766.

28. Shih A, Robertson S, Vigani A, da Cunha A, Pablo L, Bandt C. Evaluation of an indirect oscillometric blood pressure monitor in normotensive and hypotensive

anesthetized dogs. *J Vet Emerg Crit Care (San Antonio)*. 2010;20(3):313-318. doi: 10.1111/j.1476-4431.2010.00536.x.

29. Deflandre CJ, Hellebrekers LJ. Clinical evaluation of the surgivet V60046, a non invasive blood pressure monitor in anaesthetized dogs. *Vet Anaesth Analg*. 2008;35(1):13-21. doi: 10.1111/j.1467-2995.2007.00346.x.

30. Stevenson CK, Kidney BA, Duke T, Snead EC, Jackson ML. Evaluation of the accutrend for lactate measurement in dogs. *Vet Clin Pathol*. 2007;36(3):261-266.