Contract Number: W81XWH-17-P-0022
Support the (TCCCR) Task Area for Research and Development of Medical Equipment to Clear and Maintain a Combat Airway

A Report on Deliverable Two: Determine Safety Parameters [of Suction] (Primarily Maximum Vacuum Strength) That Will Not Injure Tissue

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Table of Contents

Objective of the Report

Determine the safety parameters (primarily maximum vacuum strength that will not injure tissue). This is a literature-based analysis relying on data regarding suction reported in animal and human studies. As part of this report, a study utilizing human, animal, or cadaver models will be designed and a protocol drafted that can be used to safety test a suction device. The study meets applicable ethical and legal requirements for research and may be feasibly implementable.

Background

[Readers are referred to the following for a more detailed overview and background on portable suction for use in prehospital combat casualty care: *A Report on Deliverable One: Determine Required Performance Characteristics [of Suction] for Management Of Prehospital Combat Casualty Care Injuries.* Contract Number: W81XWH-17-P-0022 Support the (TCCCR) Task Area for Research and Development of Medical Equipment to Clear and Maintain a Combat Airway. Report Author: Robert A. De Lorenzo, MD, MSCI, MSM, FACEP, Department of Emergency Medicine, UT Health San Antonio, February 22, 2017.]

Tactical airway management often determines survival in both trauma and medical patients. Skilled interventions often make the critical difference in survival for patients with actual or impending airway compromise. Managing airways in the tactical environment presents an additional level of unique and complex challenges for any emergency provider. Hazardous or confined spaces and hostile action inherently limit the ability to intervene with an artificial airway or assisted ventilation. Loss of patient airway in tactical and combat environments commonly occurs. The proximate cause can be direct trauma to the airway structures or indirectly from traumatic shock or brain injury and the subsequent loss of airway protective reflexes.

There is limited information on the types, if any, of portable suction units carried by combat medics in the far-forward combat area. Anecdotal information suggests that powered suction devices are simply too heavy to be carried in the combat medic's aid kit. Manual powered devices, while lightweight, offer limited capability and require the use of a hand or foot to operate, limiting efficiency of the provider. Fielding data from military logistics agencies on the number and types of suction units employed in the

field is not available, and prior experience suggests even if obtained, the data shows only total purchases and not where and when fielded.

Existing portable suction standards are civilian-oriented, lack a detailed base of evidentiary support, and in any case do not satisfy the critical needs of combat casualty care. Importantly, there is little data on the safety of suction units used in this setting. We will review the available literature and guidelines on suction safety with an emphasis on the maximum pressure that can be safely applied to sensitive tissue without causing harm. We will also propose a protocol draft that can be used to safety-test a suction device.

Of note, this report will focus on the safety of the patient, and not the safety aspects of the operator. That is, the operator bears some risks such as exposure to blood and body fluids by accomplishing the task of patient suctioning. This will not be addressed.

Summary of the Background Section

- The safety of suction devices is not well studied and there are no guidelines specific to the prehospital combat use of suction devices.
- This report will focus on patient safety, with an emphasis on the maximum pressure that can be safely applied to sensitive tissue without causing harm.
- Operator safety (i.e., the risk of blood or body fluid exposure) will not be addressed in this report.

Recommendations of Background Section

- None specified.

Anatomic and Physiologic Considerations of Suctioning Safety

Anatomic Considerations

Suction is the employment of negative pressure through a catheter directed into the upper airway of a casualty. The catheter can be passed through the oral or nasal cavity into the pharynx and supraglottic region. If advanced further, it can pass either into the upper esophagus or through the glottis and into the trachea. In most cases of combat casualty care the suction catheter will remain in the upper airways, as clearance of this

structure is the primary goal. Advancing the suction catheter beyond the glottis is not considered desirable when performing upper airway suction and may be detrimental by stimulating a gag reflex. In selected clinical situations, there is a need to perform tracheal suction through an endotracheal tube or similar airway device. This procedure is generally reserved for casualties undergoing lengthy evacuation as may occur in prolonged care situations. Gastric suctioning is not considered a prehospital procedure and is unlikely to be performed by a combat medic in role 1; however, it is a procedure expected in role 2 and role 3, and possibly during prolonged care.[1,2]

The tissues exposed to suctioning include all of the structures of the oro- and nasopharynx, glottis structures, trachea, and esophagus. This aerodigestive tracts has multiple functions and varied structures, each with unique characteristics relevant to suction safety. When intact and healthy, these structures have reasonable resistance to the forces generated during ordinary suctioning. Solid structures such as the teeth are impervious to the effects, while softer, mucous-membrane covered tissues can be affected. Vascularity of the aerodigestive tract likewise varies, with most soft tissue structures well supplied by superficial capillaries; larger vessels lie deeper but can also be exposed.

Since the technique of oropharyngeal suction is ideally visually guided, anatomy plays a role in creating pockets of visual obstruction. The nasal vestibule, lateral cheeks, subungual space and of course, deeper structures of the hypo- and posterior pharynx are all difficult to visualize. Large amounts of secretions and debris (often the reason for needing suction in the first place) can obscure sensitive tissues. Deeper structures such as the traches and esophagus are commonly cannulated blindly and this has additional safety implications.

Damaged or injured tissue presents additional concern as the local resistance to the forces applied can convert marginally viable to dead tissue. In rare cases avulsed tissues can be inadvertently be amputated by suctioning and exposed blood vessels can perforate, causing significant hemorrhage. Damage from trauma can also expose deeper structures to damage, and in extreme cases, result in profound iatrogenic injury. Insertion of a suction cannula into the cranium through a large basilar skull or cribiform plate fracture is one rare but serious example.

Physiologic Considerations

The activity of suctioning can have local and systemic physiologic effects. On a microscopic level, suctioning can induce tissue changes that are readily observed in pathological specimens:[3] “The vacuum effect of a surgical suction tip can induce

significant artifactual alterations in the connective tissue of specimens removed for diagnostic or therapeutic purposes. The alterations… [are] characterized by the formation of numerous, pleomorphic vacuoles that, on casual microscopic examination, resemble the morphology of traumatized adipose tissue. This artifact occurs when a vacuum draws air into connective tissue and mobilizes connective tissue mucins (acid mucopolysaccharides) that localize within the vacuoles that are formed."

If continuously applied for many minutes to hours, suction can cause local tissue ischemia and necrosis. This is a potential problem in nasogastric suctioning (gastric mucosa) and tracheobronchial suctioning (tracheal mucosa).[4,5] This was a common complication of gastric suctioning until techniques and devices became common to limit suction duration, so called intermittent-suctioning techniques.

Locally, suctioning can cause an increase in secretions secondary to tactile stimulation.[6] Generally, this effect is mild. Stimulation of sensitive tissues can result in a reflex arc such as sneezing (nasal cavity), gagging (posterior tongue), coughing (trachea), or bronchospasm (bronchi).[6] Additional reflexes include vagal stimulation with bradycardia and hypotension, and tachycardia. Elevations in intracranial pressure can also occur. Hypoxia can be the result of coughing, bronchospasm, reflex hypopnea, or the direct effect of the cannula (airway obstruction) or the evacuation of therapeutically hyperoxygenated air and its replacement with room air.

In the awake patient, suctioning can range from mildly uncomfortable to painful. Catheter stiffness, force applied and suction strength are among the factors that determine the degree of patient discomfort.[6]

Arguably the most important physiologic effect of suctioning relevant to prehospital combat care is the development of hypoxia, either directly by evacuating oxygen-enriched air from the airway, or indirectly through reflex mediated cough, laryngospasm, gagging or other mechanism.[6] Limiting the duration of suctioning, the depth of catheter insertion, and avoidance of suction airflow during periods when not in contact with fluid or debris can limit these effects.[6]

Suction in the prehospital combat casualty can be used to evacuate fluids for other than airway clearance. It can be used in virtually any part of the body. Evacuating blood for better visualization of a bleeding site is one example; evacuating skin and soft tissue abscesses is another. In these circumstances the physiologic response to suction is related to the anatomic area affected, with the most likely response being pain and discomfort. In any event, the focus of this report is on oropharyngeal suctioning for airway clearance.

Summary of the Anatomic and Physiologic Considerations of Suctioning Safety

- Anatomic consideration in suction include
    - Prehospital suctioning generally involves the aerodigestive tract
    - Structures involved include the nasal and oral cavities, naso- and oropharynx, glottic structures, trachea, bronchi, and esophagus.
    - Anatomic locations with limited visualization are at greater risk of inadvertent cannulation and local trauma.
    - Pre-existing injury or trauma can increase the risk of anatomic disruption by suctioning.
- Physiologic considerations in suction include
    - Local stimulation from suctioning can increase local secretion production
    - Reflex responses can range from sneezing (nasal cavity), gagging (posterior tongue), coughing (trachea), or bronchospasm (bronchi).
    - More serious responses include vagal-mediated bradycardia, hypotension, hypoxia, and elevated intracranial pressure.

Recommendations of the Anatomic and Physiologic Considerations of Suctioning Safety

- Training of prehospital combat casualty care providers should include the fundamentals of anatomy and physiology as they relate to the safety effects of upper airway suctioning.

Textbook Safety Techniques in Prehospital Suctioning

The technique of oropharyngeal suctioning is generally described in textbooks of prehospital, respiratory, and basic nursing care. Because the large size and heavy weight of battery powered suction units has generally precluded them from being included in the kit carried by ground combat medics, the use of powered suction devices has generally been omitted from standard texts and resources for TCCC. The sentinel 1999 textbook *Tactical Emergency Care* made reference to the management of secretions from a combat casualty through use of the recovery (lateral recumbent) position.[2] More recently, textbooks for the combat medic provide only slightly more detail on the technique of suction. For example, the 2012 US Army publication entitled *Tactical Combat Casualty Care: Lessons and Best Practices* makes no mention of suction and has just three paragraphs relevant to clearance of the airway:[7]

> *In the tactical field care phase, direct initial management to the evaluation and treatment of the casualty's airway once all hemorrhage problems have been addressed. Intervention should proceed from the least invasive procedure to the most invasive. Do not attempt any airway intervention if the casualty is conscious and breathing well on his own. Allow the casualty to assume the most comfortable position that best protects his airway, to include sitting upright.*
>
> *Unconscious casualty without airway obstruction. If the casualty is unconscious, the most likely cause is either hemorrhagic shock or head trauma. In either case, an adequate airway must be maintained. If the unconscious casualty does not exhibit signs of airway obstruction, the airway should first be opened with a chin lift or a jaw-thrust maneuver. As in the care under fire phase, cervical spine immobilization is generally not required, except in the instance of significant blunt trauma.*
>
> *If spontaneous respirations are present without respiratory distress, an adequate airway in the unconscious casualty is best maintained with a nasopharyngeal airway (NPA). An NPA is preferred over an oropharyngeal airway because it is better tolerated if the casualty regains consciousness and is less likely to be dislodged during casualty transport. After inserting the NPA, place the casualty in the recovery position to maintain the open airway and prevent aspiration of blood, mucous, or vomit.*

Another recent textbook focusing on the combat medic and tactical combat casualty care provides one of the few references to suction. It is a 2009 edition entitled *68W Advanced Field Craft: Combat Medic Skills.*[8] In the section on airway management, it describes the technique of suctioning a casualty's oropharynx. However, on careful review the information differs little from that provided in standard civilian-style emergency medical technician (EMT) textbooks from which it appears to be derived. That is, the suction technique described is exactly the same as civilian EMT textbooks with adjustments made to photos to reflect military uniforms on the providers and casualties. No additional explanation relevant to the combat situation is provided. While there is mention of preoxygneation, insertion to limited depths, and a time limit on the procedure, all related to avoiding adverse effects, there is mention of suctioning safety risks themselves.

Figure: Technique of suctioning a casualty as detailed in a combat medic textbook.

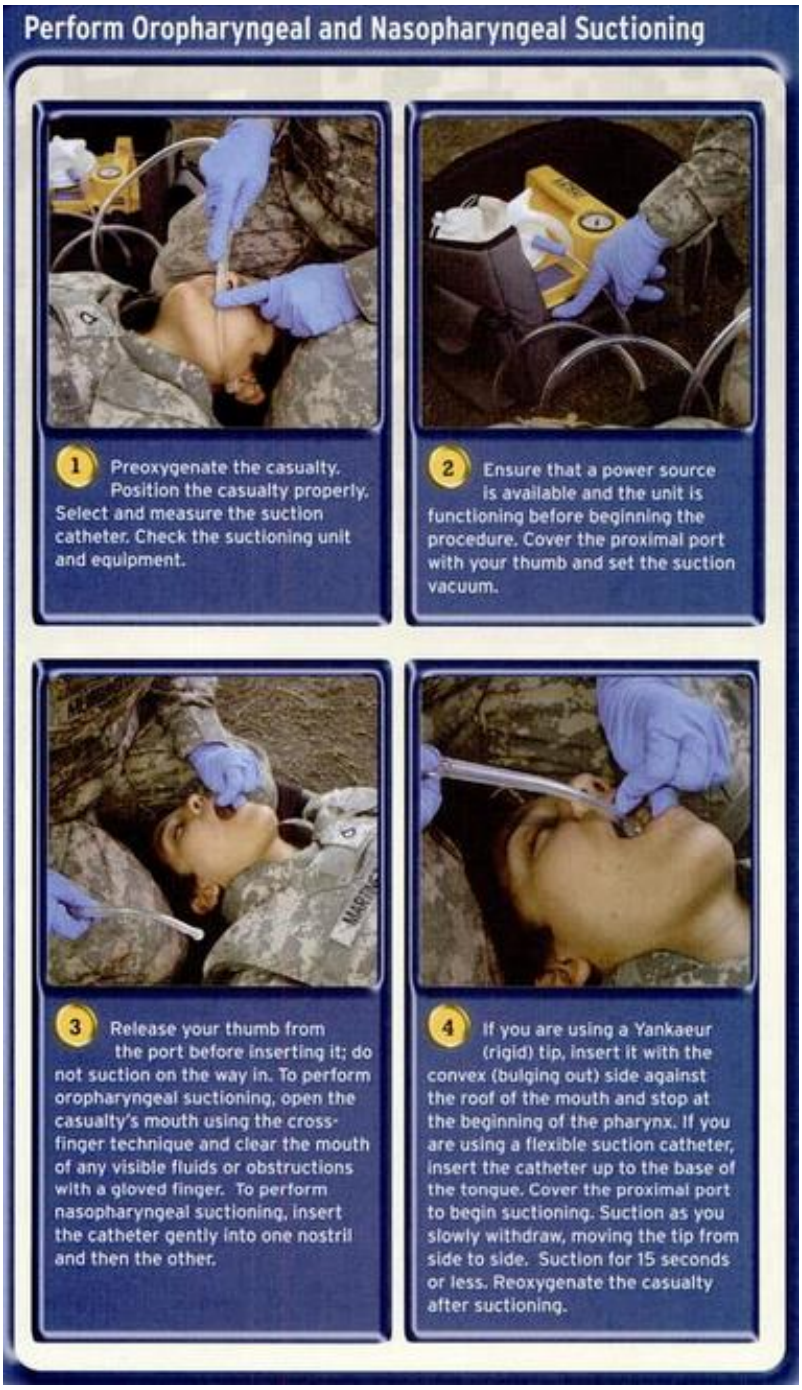

Photo Credit: US Army. 68W Advanced Field Craft: Combat Medic Skills 1st ed. Jones & Bartlett Learning; 1 edition, 2009, Burlington, MA.
COPYRIGHTED FIGURE – PERMISSION PENDING – NOT FOR PUBLICATION

A review of civilian EMT and paramedic textbooks as well as a select sample of textbooks in the fields of respiratory therapy, anesthesia, and emergency medicine reveals a paucity of safety information relevant to suctioning in tactical combat casualty care. One notable exception is Roberts and Hedges' Clinical Procedures in Emergency Medicine.[9] It notes several points related to avoidance of adverse effects in the performance of suction:

- There are no contraindications to suctioning, however prolonged (>15s) suctioning can lead to hypoxia.
- To avoid hypoxia, consider supplemental oxygen during suctioning, or hyperventilate with oxygen before suction.
- Suction only under direct vision as blind suction can cause tissue damage or convert a partial obstruction to a complete one.

Summary of the Textbook Safety Techniques in Prehospital Suctioning

- Military and tactical combat casualty care textbooks generally have limited, if any content on suction.
- Adverse effects and safety are omitted in military and tactical combat casualty care textbooks.
- Select civilian medical textbooks make pertinent recommendations relevant to suction safety and adverse effects.
    - Prolonged oropharyngeal suctioning can lead to hypoxia.
    - Hypoxia can be avoided with supplemental oxygen or pre-hyperventilation with oxygen.
    - Direct visualization is important as blind suctioning can worsen airway obstruction.

Recommendations of the Textbook Safety Techniques in Prehospital Suctioning

- Textbooks focused on combat casualty care should address the adverse effects and safety considerations of suctioning
- Recommendations on suctioning safety from select civilian medical textbooks are relevant to tactical combat casualty care and should be considered for adoption.

Peer-Reviewed Journals

There is limited peer-reviewed literature on the adverse effects of suction and related safety concerns. There are no randomized controlled trials or other high-quality evidence that addresses the issues; nevertheless there is meaningful data that can be extracted from the non-clinical studies, narrative reviews case reports, and expert opinion in the literature.

Adverse Effects

Pathophysiologically, there are several potential adverse effects of oropharyngeal and tracheobronchial suctioning,[10] and they include:

- Atelectasis
- Hypoxemia
- Pulmonary hemorrhage
- Local trauma, both from the catheter and from the vacuum-pressure aspiration of tissue
- Negative pressure pulmonary edema

Ashurst similarly summarizes the potential clinical adverse effects of airway suctioning in her review article (Table 1).[6]

Table 1 Adverse Effects of Suction, Adapted from Ashton
Discomfort and pain
Local trauma and injury
Irritation and abrasion
Hemorrhage
Perforation
Pneumothorax
Bronchospasm
Cough and sneeze
Gagging and emesis
Atelectasis
Hypoxemia
Tachycardia
Bradycardia
Hypotension
Elevated intracranial pressure

Tracheal Suctioning

Arbon, in his thesis, comprehensively summarizes the risks of endotracheal suctioning, as occurs during mechanical ventilation of a tracheal-intubated patient in a critical care unit.[10] He summarizes his position by noting that suction pressures of 150 mm Hg (with flowrates of 10-15 L air) are adequate for most clinical situations and pressures above this level have increased adverse event rates. It is critical to note that this thesis focuses on suction catheters passed through the tracheal tube and into the tracheobronchial tree. The report does not address oropharyngeal suctioning, and indeed, this latter clinical entity is vastly different than tracheobronchial suctioning through a tracheal tube.

Gastric Suctioning

Gastritis is a frequent complication of nasogastric tube insertion.[11] Pressure and irritation of the stomach by the tip of the tube have been implicated, as opposed to the action of aspirated tissue by the induced vacuum.[12] In any event frequent changing of the tip position and use of intermittent suction should minimize incidence of gastritis in patients with nasogastric tubes in place. Regardless of the recommendations, the implication for prehospital oropharyngeal suctioning is not clear.

Suction Vacuum Pressure Levels

Carroll, in 2003, noted: “There is little research to guide the clinician in selecting appropriate level of negative pressure for various suctioning procedures. For example, a review of published (but not referenced) guidelines for airway suctioning found suggested levels of 50 to 100 mm Hg for infants, 80 to 120 mm Hg for children, and 100 to 150 mm Hg for adults. However, none of these recommendations are evidence-based.[13] Additionally, these generic recommendations do not take into account the type of suctioning (e.g., tracheobronchial or oropharyngeal), the clinical indication, or the particular catheter used or flowrates desired. To date there has not been significant additions to the literature base on this topic.

Summary of the Peer-Review Journals Section

- There are no studies or expert opinions regarding the adverse effects or safety of suction units intended for prehospital oropharyngeal suctioning.
- There is limited information to support the premise that rigid catheters are more likely to cause local tissue trauma than flexible catheters.

- There is no data to guide the maximal vacuum pressure or flow rates that can be safely applied for prehospital oropharyngeal airway suctioning.
- There is expert opinion on maximal vacuum pressure ranges for tracheal suctioning.
- Reports on gastric suctioning vacuum pressure maximums and duration of suction application have limited translation to prehospital airway clearance and may be misleading.

Recommendations of the Peer-Review Journals Section

- Standards should be established relevant to the safety of prehospital combat casualty care suctioning including:
    - Suction catheter rigidity and ability to cause trauma to airway structures
    - Maximal suction flow rate
    - Maximal vacuum pressure

Manufacturing Standards on Suction Device Safety

A review of the available literature reveals no standards, either proposed, validated or accepted for the safety or avoidance of adverse effects portable suction devices for use in combat casualty care. Similarly, there are no accepted standards to guide the safe use and anticipated adverse effects of suction for use in prehospital or emergency care. There are, however some sources that inform the discussion.

ISO 10079-1 Medical Suction Equipment

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. ISO typically focuses on technical and engineering aspects of a machine and in general, they do not address medical standards, *per se*. ISO is generally used by manufacturers seeking to document they have produced products that have met certain standardization guidelines. ISO is not normally considered applicable to the actual practice of patient care in the clinical environment.

ISO 10079 is a standard with the most recent available date of 2014-15 (the range reflects the different subparts of the ISO document).[14,15,16] Compliance with ISO is voluntary but generally expected since a governmental body (e.g., Food and Drug Administration) requires it.

It is important to recognize that ISO 10079 covers suction devices in general, that is, it encompasses the universe of all medical suction devices. Suction devices for use in prehospital care are just a subset and not all of ISO 10079 is relevant to this environment, let alone combat. In fact, much of the ISO standard represents good manufacturing practice, safety standards, and design implications that would all likely be transparent to the clinician. Nevertheless, the standard contains a number of relevant patient safety requirements for portable suction devices that may or may not apply to the combat casualty care environment. A select list of characteristics follows; readers are referred to the full ISO document for additional details.

ISO 10079 represents a minimum standard for portable manual and electrically powered suction devices. There is little indication in the standard that these minimums are satisfactory patient safety parameters for either prehospital or combat casualty care use.

A large manufacturer of medical suction devices publishes a guide entitled “The Principles of Vacuum and Clinical Application in the Hospital Environment.”[12] It provides this nonspecific safety guidance: “The clinician must be cautious when determining the amount of negative pressure applied to the patient. The minimum amount of negative pressure necessary to accomplish the suctioning procedure should be used. When additional flow is necessary, changes in other suction variables, such as tubing length and diameter should be considered before increasing negative pressure.” For airway suctioning, it provides this additional recommendation, but does not provide the evidentiary support: “Keep pressure below 80-120 mmHg; Make sure outer diameter of catheter is; no more than half the inner diameter of airway; Give supplemental oxygen and deep breaths.”

Food and Drug Administration Regulations

The Food and Drug Administration (FDA) classifies medical devices according to their hazard risk.[17] Devices are classified into one of three categories—Class I, Class II, and Class III. Class I devices are deemed to be low risk and are therefore subject to the least regulatory controls. Class II devices are higher risk devices than Class I and require greater regulatory controls to provide reasonable assurance of the device’s safety and effectiveness. Class III devices are generally the highest risk devices and are therefore subject to the highest level of regulatory control. Class III devices must typically be approved by FDA before they are marketed. Class II devices are subject to much more stringent regulations that that of a Class I device.

Powered suction devices are considered a class II device by the FDA. Below are the several devices related to emergency suction devices and their classification.

Device Nomenclature	Regulation Number	Class
Patient care suction apparatus	870.5050	II
Catheter and tip, suction	880.6740	II

Class II devices are medical devices which pose a higher level of risk to a patient and as such require additional regulation to ensure the safety and effectiveness of the device. Class II medical devices are devices, which if they fail, can cause injury but not death to a patient who uses them. The regulatory controls that are put into place include a premarket authorization, post market analysis, and adherence to national and international performance standards.

There are no specific FDA guidelines or regulations regarding emergency suction devices in terms of patient safety or avoidance of adverse effects.

Summary of the Manufacturing Standards for Suction Device Safety Section

- Suction devices are FDA class II
- ISO 10079 provides detailed manufacturing standards for suction devices intended for use in emergency and prehospital care.
- However, ISO 10079 does not adequately inform patient safety or the avoidance of adverse effects of suction.
- At least one suction device manufacturer provides generic safety recommendations but does not present evidentiary support.

Recommendations of the Manufacturing Standards for Suction Device Safety Section

- Establish clinical (patient) safety standards for suction use in prehospital and far-forward combat casualty care environments.

Summary and Conclusions

Suction is a critical component of airway management, which is the second leading cause of preventable battlefield death. Current commercially available portable suction devices have not been scientifically validated for key performance measures relevant to patient safety. Adverse effects of oronasopharyngeal suction for airway clearance

include local tissue trauma as well as systemic effects of such as hypoxemia or atelectasis. While there are recommendations and guidelines for tracheobronchial and nasogastric suctioning, there are no comparable recommendations for oronasophayngeal suctioning. Non-evidence based assertions on safety do exist, but these cannot be recommended owing to the lack of validity. Nevertheless, existing guides and recommendations, such as those in textbooks of prehospital care do not appear outside the bounds of reasonableness and are unlikely to be harmful in and of themselves. Whether they are necessary for patient safety will have to wait further evidence. In the interim, there appears little evidence for or against different levels of vacuum pressure, air flow rates, or catheter design.

Acknowledgements

The author wishes to acknowledge the administrative and editorial skill, tireless effort and patience of Heather Wantuch, MPA; and the technical advice, support and background information of Bruce Adams, MD, Yusheng Feng, PhD, and Lyle Hood, PhD.

Appendix A - Section Summaries and Recommendations

Summary of the Background Sections

- The safety of suction devices is not well studied and there are no guidelines specific to the prehospital combat use of suction devices.
- This report will focus on patient safety, with an emphasis on the maximum pressure that can be safely applied to sensitive tissue without causing harm.
- Operator safety (i.e., the risk of blood or body fluid exposure) will not be addressed in this report.

Recommendations of Background Section

- None specified.

Summary of the Anatomic and Physiologic Considerations of Suctioning Safety

- Anatomic consideration in suction include
    - Prehospital suctioning generally involves the aerodigestive tract
    - Structures involved include the nasal and oral cavities, naso- and oropharynx, glottic structures, trachea, bronchi, and esophagus.
    - Anatomic locations with limited visualization are at greater risk of inadvertent cannulation and local trauma.
    - Pre-existing injury or trauma can increase the risk of anatomic disruption by suctioning.
- Physiologic considerations in suction include
    - Local stimulation from suctioning can increase local secretion production
    - Reflex responses can range from sneezing (nasal cavity), gagging (posterior tongue), coughing (trachea), or bronchospasm (bronchi).
    - More serious responses include vagal-mediated bradycardia, hypotension, hypoxia, and elevated intracranial pressure.

Recommendations of the Anatomic and Physiologic Considerations of Suctioning Safety

- Training of prehospital combat casualty care providers should include the fundamentals of anatomy and physiology as they relate to the safety effects of upper airway suctioning.

Summary of the Textbook Techniques in Prehospital Suctioning

- Military and tactical combat casualty care textbooks generally have limited, if any content on suction.
- Adverse effects and safety are omitted in military and tactical combat casualty care textbooks.
- Select civilian medical textbooks make pertinent recommendations relevant to suction safety and adverse effects.
    - Prolonged oropharyngeal suctioning can lead to hypoxia.
    - Hypoxia can be avoided with supplemental oxygen or pre-hyperventilation with oxygen.
    - Direct visualization is important as blind suctioning can worsen airway obstruction.

Recommendations of the Textbook Techniques in Prehospital Suctioning

- Textbooks focused on combat casualty care should address the adverse effects and safety considerations of suctioning
- Recommendations on suctioning safety from select civilian medical textbooks are relevant to tactical combat casualty care and should be considered for adoption.

Summary of the Peer-Review Journals Section

- There are no studies or expert opinions regarding the adverse effects or safety of suction units intended for prehospital oropharyngeal suctioning.
- There is limited information to support the premise that rigid catheters are more likely to cause local tissue trauma than flexible catheters.
- There is no data to guide the maximal vacuum pressure or flow rates that can be safely applied for prehospital oropharyngeal airway suctioning.
- There is expert opinion on maximal vacuum pressure ranges for tracheal suctioning.
- Reports on gastric suctioning vacuum pressure maximums and duration of suction application have limited translation to prehospital airway clearance and may be misleading.

Recommendations of the Peer-Review Journals Section

- Standards should be established relevant to the safety of prehospital combat casualty care suctioning including:
    - Suction catheter rigidity and ability to cause trauma to airway structures
    - Maximal suction flow rate
    - Maximal vacuum pressure

Summary of the Manufacturing Standards for Suction Devices for Use in Combat and Emergency Care Section

- Suction devices are FDA class II.
- ISO 10079 provides detailed standards for suction devices intended for use in emergency and prehospital care.
- There are minimum performance standards for suction devices but they have not been validated clinically or operationally, and may be inadequate for emergency and prehospital care.
- The standards are unlikely to be applicable to combat casualty care environments.

Recommendations of the Manufacturing Standards for Suction Devices for Use in Combat and Emergency Care Section

- Establish clinical standards for suction use in prehospital and far-forward combat casualty care environments.

Summary of the Textbooks in Prehospital Combat Casualty Care Section

- Military and tactical combat casualty care textbooks generally omit suction as a topic.
- Select civilian medical textbooks make pertinent recommendations relevant to suction performance and characteristics.
    - Large bore tips and tubing improve suction performance.
    - Prolonged suctioning can lead to hypoxia.
    - Hypoxia can be avoided with supplemental oxygen or pre-hyperventilation with oxygen.
    - Clogging is a frequent problem but can be mitigated with traps.
    - Direct visualization is important as blind suctioning can worsen airway obstruction.
    - Equipment should be readily deployable for patient use.

Recommendations of the Textbooks in Prehospital Combat Casualty Care Section

- Textbooks focused on combat casualty care should address suctioning.
- Recommendations from select civilian medical textbooks are relevant to tactical combat casualty care and should be considered for adoption.

Summary of the Peer-Review Journals Section

- There are no studies or expert opinions regarding the appropriate size and weight of portable suction units intended for prehospital care.
- Similarly, there is no data on vacuum suction pressure or flow rates.
- The Yankauer tip and small diameter tubing is ineffective for emergency care suction.

- Large bore tips and tubing improve suction performance.
- There is not a standardized fluid viscosity to test suction performance but investigators have used a range of simulated emesis fluids.
- There are no standards on particulate matter but experts opine that removal capacity is an important attribute of suction devices.
- Container capacity is not studied but ranges from 140 – 1000 mL.
- Reliability of suction machines may be inadequate; there is no data on ergonomics.
- There is no information on the specific needs of the tactical environment including ruggedness, and light and noise abatement.

Recommendations of the Peer-Review Journals Section

- Standards should be established relevant to combat casualty care for
    - Size and weight of portable suction machines
    - Suction tip and tubing diameter
    - Minimum performance especially flowrates of validated simulated emesis t
    - Effluent container capacity
    - Reliability, ruggedness, and ease of use, and ergonomics
    - Noise and light abatement

Summary of the Manufacturing Standards for Suction Device Safety Section

- Suction devices are FDA class II
- ISO 10079 provides detailed manufacturing standards for suction devices intended for use in emergency and prehospital care.
- However, ISO 10079 does not adequately inform patient safety or the avoidance of adverse effects of suction.
- At least one suction device manufacturer provides generic safety recommendations but does not present evidentiary support.

Recommendations of the Manufacturing Standards for Suction Device Safety Section

- Establish clinical (patient) safety standards for suction use in prehospital and far-forward combat casualty care environments.

Appendix B - Key Task of the Report

Determine safety parameters (primarily maximum vacuum strength that will not injure tissue). This will be a literature-based analysis relying on data regarding suction reported in animal and human studies. As part of this effort, a study utilizing human, animal, or cadaver models will be designed and a protocol drafted to safety test a suction device. The The study must meet applicable ethical and legal requirements for research and be feasibly implementable. Deliverables will be : 1) A report of safety parameters, and 2) Written protocol of study that is ready for regulatory review.

Appendix C - Technical Approach

Existing and projected (future) military medical requirements relevant to the expected combat and operational scenarios (such as prolonged field care) are identified. The required performance characteristics of a suction unit intended for prehospital combat casualty care is ascertained based on these anticipated operational scenarios. The key characteristics searched include vacuum suction flow rate, pressure, and capacity to evacuate the expected fluid/particle viscosity/size (e.g., saliva, blood, vomitus, mud, gravel, broken teeth) for management of prehospital Combat Casualty Care injuries. Source documents were extracted from 1980-present and analyzed for title content. If relevant, the article was reviewed in detail. Secondary references prior to 1980 were selectively searched based on the title and the likelihood of topical relevance. Specific sources searched include but are not limited to:

- Committee on Combat Casualty Care (CoTCCC)
- Medical literature using Medline or equivalent with search terms including
    - *Suction*
    - *Vacuum*
    - *Aspiration*
    - *Airway, airway management*
    - *Airway obstruction*
    - Modifier terms including *safety, efficacy, and performance*
- Engineering literature using Academic Search (EBSCO), or equivalent using similar search terms as above
- Defense Technical Information Center (DTIC)
- Retrievable information from conferences and meetings focused on combat casualty care, prehospital care, and airway management.
- Government standards including FDA
- Industry and government standards clearinghouses including ISO

Where necessary to fill in information gaps, existing requirements were supplemented with proposed requirements vetted against local expert military and civilian medical consultations. UT Health San Antonio maintains a robust panel of US military experts in emergency medicine and prehospital care that can be consulted. Additionally, UT

Health San Antonio is in close proximity to and maintains a healthy relationship with JBSA-Fort Sam Houston which is the US military's key hub of combat casualty care and trauma training, and UT Health San Antonio retains the ability to consult with the organizations and personnel within this installation as well as other US military installations worldwide.

The available information is organized, critically appraised, and synthesized into a narrative report that summarizes the performance characteristics for management of prehospital combat

Appendix D – Proposed Research Protocol to Test Suction Safety

PROTOCOL TITLE: Prehospital Upper Airway Suctioning Clinical (Patient) Safety – A Test of Catheter Flexibility, Suction Vacuum Pressure, and Flowrate on Local Tissue Damage

BACKGROUND

Study Aim: The primary goal of this study is to explore key clinical safety issues regarding suction use in airway clearance in the prehospital combat casualty care environment. For purposes of this protocol, the following parameters and assumptions are established:

- Scope is limited to the clinical application of suctioning the oronasopharyngeal airway for purposes of airway clearance for basic life support of in preparation for advanced airway procedures such as orotracheal intubation.
- Mechanisms of potential injury will focus on local trauma as a result of catheter mechanics and/or vacuum pressure effects and flowrates.
- Not examined are systemic or distant effects such as hypoxemia or atelectasis.

Background and Review of the Literature: Tactical airway management often determines survival in both trauma and medical patients. Skilled interventions often make the critical difference in survival for patients with actual or impending airway compromise. Managing airways in the tactical environment presents an additional level of unique and complex challenges for any emergency provider. Hazardous or confined spaces and hostile action inherently limit the ability to intervene with an artificial airway or assisted ventilation. Loss of patient airway in tactical and combat environments commonly occurs. The proximate cause can be direct trauma to the airway structures or indirectly from traumatic shock or brain injury and the subsequent loss of airway protective reflexes.

In the Vietnam War, 6% of all soldiers killed in action only had an airway obstruction. More recent conflicts, notably Operation Iraqi Freedom (OIF), have shown an increase in primary injuries to the airway. In OIF, 27% of wounded in action suffered injuries only to the head, neck or airway structures.[18] This increase in airway trauma is likely due to the excellent torso protection of body armor and a subsequent diversion of injuries towards less armored areas such as the neck and face. The Registry of Emergency Airways at Combat Hospitals study (REACH) shows that prehospital cricothyrotomies are performed ten times more often on the battlefield as compared to civilian trauma systems. (5.8% vs. 0.5%).**Error! Bookmark not defined.** A recent study highlights the high incidence of combat airway injury in combat maxillofacial trauma.[19] In these and other trauma cases, airway management requires a low threshold for airway stabilization to include tracheal intubation and cricothyrotomy or tracheostomy. A major reason for this dramatically higher rate of surgical airways is poor visualization of the injured airway with current inadequate suction devices available on the battlefield.

Aspiration of as little as 25 mL (approximately ¼ mouthful) of vomitus can cause significant pulmonary aspiration injury, and a massive aspiration carries a mortality as high as 70%.[20,21] Delays in suction can presumably increase the risk of aspiration, obstruction-related hypoxia, and make visualized intubation of the trachea impossible, so the availability and performance of suction can be viewed as essential. Despite this, there is a paucity of high-quality evidence on the techniques of suction. A 2009 Cochrane review on suctioning of patients revealed limited scope of data.[22] Practice guidelines from 2001 on hyperoxygenation, hyperinflation, use of a ventilator circuit adaptor and subglottic suctioning were validated. In the review, new evidence was identified with respect to indications for suctioning, open suction versus closed suctionsystems, use of medications and infection control. Virtually all of the data was focused on in-hospital suctioning of primarily mechanically ventilated patients. There were no high-quality reports focusing on prehospital or emergency care in the Cochrane review.

The combat experience of the last dozen years clearly demonstrates that airway obstruction is the leading cause of preventable combat casualty deaths behind only hemorrhagic shock. Between 6-10% of battlefield deaths could have been prevented with adequate airway management.[23] Because of vastly improved body armor and the enemy's shift towards direct fire and improvised explosive devices, the injury pattern today is much different than in previous wars. Airway management in this austere environment is notoriously difficult for many reasons but especially because of inadequate airway equipment.

Nonhuman primates are considered the standard model for the human airway, but these species are not available for study. Large animals such as swine approximate adult human cardiorespiratory physiology, but lack anatomic correlation. Smaller animals such as cats and ferrets have anatomy similar to small children, but this is not the population of interest. Given the overall experimental situation, the most pragmatic compromise is a young swine. It is available, cost-effective, and offers reasonable local tissue similarity in the areas of interest.

Significance: In comparison to the advances in many areas of prehospital equipment, the current suction devices on the market have not achieved the level of performance required in civilian prehospital care, let alone battlefield care. It is telling that a recent 5 page review article on an advances in technology and concepts in tactical combat casualty care, there was no mention of suction and had only this to say about airway management advances in general:

Airway Protection: A skill common to all physicians deploying on the MERT Medical Emergency Response Team (MERT)] is that they must be proficient at airway assessment and competent to definitively secure an airway if required. Generally, this takes the form of a rapid sequence induction using direct laryngoscopy. Several rescue devices are also available as alternatives or for use in a failed intubation such as supraglottic airways, optical laryngoscopes, and cricothyroidotomy.

Perhaps reflecting the perceived lack of effectiveness of prehospital suction devices, Kozak reported on a survey of paramedics carrying suction equipment to the scene of medical aid calls less than 25% of the time, and once on scene, suction equipment was utilized on only 50% of advanced airway procedures. It seems the available off-the-shelf devices do not possess the proper balance of tradeoffs between portability, effectiveness and cost to be effective in tactical care.

To help answer questions regarding clinical safety of upper airway suctioning in the prehospital combat environment, a series of large animal experiments are proposed to test selected safety issues: mechanisms of potential injury will focus on local trauma as a result of catheter mechanics and/or vacuum pressure effects and flowrates. Not examined are systemic or distant effects such as hypoxemia or atelectasis.

Literature Sources Searched: Literature review was completed with the assistance of a librarian. The databases searched included: Biomedical Research Database (BRD), Computer Retrieval of Information of Scientific Projects (CRISP), Federal Research in Progress (FEDRIP), Defense Technical Information Center (DTIC), Pub Med/Medline and OVID.

Key Words of Search: Suction; Vacuum; Aspiration; Catheter, Airway; Oropharyngeal; Nasopharyngeal, Tracheal; Safety; Adverse Effects. Boolean combinations and fuzzy logic were used as allowed by the search engines.

Results of Search: No previous or ongoing duplicative research was noted. Relevant to the proposed animal model, the literature search did reveal several examples of using this particular species for conducting suction studies, as noted below.

OBJECTIVE/HYPOTHESIS:

Research Questions: Does the technique of suction use in airway clearance in the prehospital combat casualty care environment entail safety risks to the patient regarding local trauma from a) varying suction catheter mechanics, b) different levels of vacuum pressure and flowrates.

Primary Hypothesis: High vacuum pressures and long contact time will result in minor local tissue damage to sensitive oronaospharyngeal tissues, but major damage will not occur.

Secondary Hypotheses: Stiff and sharp suction catheters will result in minor local tissue damage to sensitive oronaospharyngeal tissues, but major damage will not occur.

MILITARY RELEVANCE:

There is limited information on the types, if any, of portable suction units carried by combat medics in the far-forward combat area. Anecdotal information suggests that powered suction devices are simply too heavy to be carried in the combat medic's aid kit. Manual powered devices, while lightweight, offer limited capability and require the use of a hand or foot to operate, limiting efficiency of the provider. Fielding data from

military logistics agencies on the number and types of suction units employed in the field is not available, and prior experience suggests even if obtained, the data shows only total purchases and not where and when fielded.

Existing portable suction standards are civilian-oriented, lack a detailed base of evidentiary support, and in any case do not satisfy the critical needs of combat casualty care. We propose a set of performance standards that meet the needs of prehospital combat casualty care that could support a future development of a portable suction design that meets all of the combat medic's needs.

MATERIALS AND METHODS

Experimental Design and General Procedures

Training / Model Development (n = 6): Up to six animals will be used for training research personnel and for establishing and standardizing the experimental methodology described below. The same procedures will be performed in the model development animals as is noted for experimental animals. If determined feasible, data collected during model development will be used for experimental purposes and will be included for purposes of statistical comparison. Doing so will maximize individual animal use and also reduce the total number of animals required. Only those animals needed for model development will be used. A report of the results of the model development will be provided to the IACUC prior to proceeding with the experimental methodology.

Experimental Methodology (n = X): Up to X pigs, weighing 30 – 45 kg, will be used in this acute non-survival study. Animals will be fasted overnight the day prior to experimental use. Buprenorphine (0.01mg/kg) will be used for pre-emptive analgesia and administered intramuscularly approximately one hour prior to anesthetic induction. For purposes of induction, animals will be tranquilized with Telazol® (4-6 mg/kg IM) administered through a 20 - 22 gauge x 1" butterfly catheter (or similar) in the dorsolateral cervical area. The animals will then be masked down, intubated with a cuffed endotracheal tube, and anesthesia maintained with 2-3% isoflurane. Aural catheters will be placed in one or both ears in order to establish vascular access. A Foley catheter will be placed into the bladder for monitoring urinary output. Ventilator settings will be set to deliver 100% oxygen at 10-12 breaths per minute with a tidal volume of 6 cc/kg. Settings will be adjusted as necessary to maintain an end tidal pCO_2 of 40±5 mmHg. Body temperature will be monitored with a rectal probe and maintained in the normal range (38-39°C) using passive insulation, a heated surgical table, circulating water blankets, and/or forced warmed air (Bear-Hugger®). All anesthetic procedures will be performed by research or veterinary personnel in accordance with American Society of Anesthesiologist (ASA) standards.

Applicable Study Monitoring: Standard veterinary anesthesia monitoring with particular experimental interest in systemic hypoxia as measure by pulse oximetry.

Interventions: Once a general plane of isoflurane anesthesia is established the experiments will commence. A matrix of vacuum pressures, contact times, suction catheter types and tip diameters, axial loading forces, and tissue types will be systematically examined.

- Vacuum pressure 50mm Hg to 760 mm Hg (1 atmosphere) in 100 mm Hg increments.
- Air flowrates of 1, 5, 10 15 and 20 L/min of air.
- Contact times of 10s, 30s, 60s, 90s, 120s, and then in 1 min increments up to 5 min.
- Suction catheters of various types marketed for prehospital use will be tested.
- Axial loading forces and velocities representing the range expected from human manual manipulation of the catheter will be applied to specified locations to determine risk of minor and major injury.
    - Sublingual
    - Peri-uvular
    - Paraphyryngeal space overlying the carotids
    - Aretynoid fossa

Visual Determination of Injury: Standard pathological gross grading scales for local tissue trauma will be used. Bleeding will be graded as minor (oozing), moderate (obvious flow but easily controllable with direct pressure, and severe (obvious flow and not easily controlled with direct pressure).

Histopathological Determination of Injury: Standard histological grading scales for local tissue trauma will be used.

Data Analysis: This is primarily a preliminary investigation and descriptive statistics will be used, supplemented with regression analysis to seek associations for future study. Quantitative means can be used in follow-on experiments once specific parameters are known and comparative measures can be instituted.

Estimation of Sample Size: The general rule for regression analysis is that there should be 30 to 100 correlations distributed across the range of interest. The general rule for multivariate analysis is that there should be 10 to 30 correlations per independent variable. The regression model is expected to have 5 independent variables. The five most significant independent variables will be selected by Spearman rank correlation. With 5 independent variables, there will need to be 50 to 150 observations. A sample size of 8, with data collection at baseline and then every 15 minutes thereafter, should provide ~18 time points and thus a total of 144 correlations.

Non-animal Alternatives Considered: Non-animal alternatives were considered, however, since the objective of this effort involves complex anatomic and physiological interactions in response to life threatening hemorrhage, non-animal models are unacceptable. There are no computer models to simulate the anatomic and physiological responses to airway suctioning. Furthermore the development of the

present model is to provide adequate information to justify subsequent evaluation of products in human patients with traumatic injuries.

Animal Model and Species Justification: A review of the literature shows the swine model is preferentially used by investigators seeking anatomic and physiologic data relevant to the present study. Other species have been used including dogs, cats, goats and sheep. Rodents and lagomorphs are frequently used because their small size correlates well to human pediatric airway anatomy. A pig model has further advantages in that it is widely accepted as a training model for selected airway procedures and is an acceptable basic science model of cardiorespiratory physiology.

Laboratory Model Genus and Species: *Sus scrofa*

Breed/Strain/Stock: Yorkshire

Vendor: Approved USDA licensed vendor.

Age: Age appropriate for weight range specified

Weight: 30-45 kg

Sex: Female animals are preferred due to ease of urinary catheterization.

Special Considerations: Animals should be free of primary porcine pathogens (e.g., viral, mycoplasmal, bacterial, etc.) and, in addition, be internal and external parasite free (helminth, protozoal, arthropods) and absent from any physical abnormalities.

Refinement, Reduction, Replacement

Refinement: The literature offers no indication of methods for refinement of potentially painful or distressful procedures beyond maintaining adequate anesthesia and analgesia. Procedures will be conducted in a state-of-the-art surgical suite with modern instrumentation by experienced veterinarians and research staff. Emphasis upon relief of stress, anxiety and pain will be provided in an AAALAC accredited animal facility. A dedicated transport cage will be utilized for the movement of all animals. This device minimizes handling stress and provides minimal restraint that is safe for both animals and personnel. Prior to proposed procedures, all animals will receive preemptive analgesia followed by induction of general anesthesia. Animals will be maintained in a surgical plane of anesthesia during all procedures. No other refinement methods were considered for use in this protocol.

Reduction: The fewest number of animals necessary to accomplish the experimental objectives and give statistically significant results have been requested. Multiple correlations will be calculated from the measured variables. Since power analysis is not considered statistically appropriate for regression analysis, animal numbers were estimated by using general statistical rules for determining correlation. By careful monitoring of return to baseline hemodynamic states, each animal in this study will be

used as its own control, thereby minimizing the number of animals required. Animals will be transferred from other protocols if possible.

Replacement: The use of non-animal systems, such as cell cultures, are inappropriate for this proposed study as they would not allow accomplishment of the experimental objectives. The pig represents the least sentient species that approximates the airway environment of humans and enables the successful use of suction catheters in various anatomic locations.

Technical Methods

Pain/Distress Assessment: In accordance with Animal Welfare Regulations, the Attending Veterinarian was consulted in the planning of procedures and manipulations outlined in this protocol.

Anesthesia/Analgesia/Tranquilization: Following overnight fasting, with water having been made continually available, buprenorphine (0.01mg/kg) will be administered intramuscularly by the veterinary staff, for pre-emptive analgesia, approximately one hour prior to anesthetic induction. For purposes of induction, animals will be tranquilized with Telazol® (4-6 mg/kg IM) administered through a 20 - 22 gauge x 1" needle or similar (butterfly catheter) or another appropriate anesthetic regimen approved by the attending or staff veterinarian. Injection volumes exceeding 6.0 ml will be administered in multiple sites. Following induction, the pig will be intubated with an endotracheal tube and a surgical plane of anesthesia established and maintained using isoflurane inhalant anesthetic (2 – 3%), delivered in 100% oxygen. An 18 – 22 gauge aural catheter will be placed in one or both ear veins to establish venous access. The animals will remain anesthetized during all experimental procedures, including catheter placement for vascular access.

All induction and anesthesia administration will be standardized as per kg body weight in all animals and performed by a staff veterinarian, trained veterinary technicians, or by the research staff. Anesthetic depth will be monitored throughout all procedures. Vital function parameters, core body temperature (38 – 39°C), pulse (105±10), respiration (20±3), mean arterial blood pressure (102±9 mmHg), arterial pO2 (71±3mmHg), and arterial pCO2 (40 ± 5 mmHg) will be recorded in the animal's medical record every 15 minutes.

Pre-procedural Provisions: After arrival to the animal facility, and a minimum 72-hour acclimation period, not counting the day of arrival, animals will be lightly anesthetized with 4 – 6 mg/kg IM tiletamine-zolazepam (Telazol®) and blood samples (20 ml) collected from the anterior vena cava by veterinary staff for baseline hematologic data [CBC, blood chemistry (sodium, potassium, chloride, LDH, AST, ALT, ALK phos, albumin, total protein, glucose, CK, total bilirubin, creatinine, BUN]. This data will be used by the veterinary staff to assess the health of the animals. Following overnight fasting, with water being continuously available, on the day of the planned procedure, preemptive analgesia (buprenorphine hydrochloride – 0.01 mg/kg IM) will be

administered, by veterinary technical staff, approximately 1 hour prior to anesthetic induction.

Post-procedural Provisions: This protocol is an acute, non-survival protocol. All animals will be immediately euthanized upon completion of experimental procedures while still under general anesthesia.

Paralytics: None

Literature Search for Alternatives to Painful or Distressful Procedures:

Sources Searched: Medline, DTIC, CRISP, BRD, FEDRIP, AGRICOLA

Key Words of Search: Suction; Vacuum; Aspiration; Catheter, Airway; Oropharyngeal; Nasopharyngeal, Tracheal; Safety; Adverse Effects. Boolean combinations and fuzzy logic were used as allowed by the search engines.

Results of Search: No alternatives were found to the potentially painful/distressful procedures proposed in this study (all noted procedures will be performed under general anesthesia).

Pre-surgical Provisions: After arrival to the animal facility, and a minimum 72-hour acclimation period, not counting the day of arrival, animals will be lightly anesthetized with 4 – 6 mg/kg IM tiletamine-zolazepam (Telazol®) and blood samples (20 ml) collected from the anterior vena cava by veterinary staff for baseline hematologic data [CBC, blood chemistry (sodium, potassium, chloride, LDH, AST, ALT, ALK phos, albumin, total protein, glucose, CK, total bilirubin, creatinine, BUN]. This data will be used by the veterinary staff to assess the health of the animals. Following overnight fasting, with water being continuously available, on the day of the planned procedure, preemptive analgesia (buprenorphine hydrochloride – 0.01 g IM) will be administered, by veterinary technical staff, approximately 1 hour prior to anesthetic induction.

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Post-surgical Provisions: This protocol is an acute, non-survival protocol. All animals will be immediately euthanized upon completion of experimental procedures while still under general anesthesia.

Location: ALAC-Approved vivarium

Injections: None

Biosamples: None other than previously specified.

Adjuvants: None

Monoclonal Antibody (MAbs) Production: None

Animal Identification: Cage cards and ear tags will be used for animal identification. Any gross identifying marks or characteristics will also be noted in each animal's medical record and on the cage card.

Behavioral Studies: None

Other Procedures: None

Tissue Sharing: Upon request by other Principal Investigators and upon completion of the required paperwork, after reaching their specified study endpoint animals may be transferred, while being maintained under general anesthesia, to other IACUC-approved protocols (for terminal use only).

Study Endpoint: The study endpoint for all animals is euthanasia at the time data collection is completed (approximately 280 minutes from baseline). At this time animals will immediately be euthanized while under general anesthesia. If at any time, prior to animals' reaching their specified study endpoint, they show any indication of pain and/or distress, a staff veterinarian will immediately be consulted. If the pain and/or distress cannot be promptly alleviated, they will immediately be euthanized. Additionally, as an alternative to death as an endpoint, animals will immediately be euthanized if their MAP reaches 20 mmHg for > 5 minutes or an end tidal CO_2 of <15 mmHg is noted.

Euthanasia: Animals reaching their specified study endpoint, or if they experience any pain and/or distress that cannot be promptly relieved, will immediately be euthanized IAW the 2007 AVMA Guidelines on Euthanasia. Euthanasia will be accomplished with a commercial euthanasia solution (e.g., Fatal-Plus® or similar) given intravenously at the label dose (~1 ml/ 4.5kg body weight) Death will be confirmed by lack of heartbeat (ECG tracing and/or auscultation) and lack of observed spontaneous respirations for a period of 3 minutes.

Veterinary Care

Husbandry Considerations: All animals will be housed and cared for IAW the ILAR *Guide for the Care and Use of Laboratory Animals* and all applicable Federal, state, and local regulations. The vivarum facility is fully accredited by the Association for the

Assessment and Accreditation of Laboratory Animal Care, International (AAALAC, Intl.). Husbandry will be provided by trained animal care staff in accordance with standard operating procedures. They will be held a minimum of 72 hours after receipt for acclimation / stabilization purposes prior to being used for research. Animal housing environmental conditions are controlled by a dedicated HVAC system engineered and maintained to meet ILAR Guide recommendations. Conditions are monitored with the use of the Watchdog® Environmental Monitoring System. All animals will receive laboratory grade commercial swine feed. Water is provided ad libitum to all animals via an automated water delivery system (lixits).

Routine Veterinary Medical Care: Animals will be evaluated, at least twice daily, including weekends, by both animal caretakers and veterinary technical personnel. If an animal appears ill or debilitated, the Vivarium technicians and/or staff veterinarian will be immediately notified and appropriate action will be taken to diagnose and alleviate the problem. If at any time an animal is determined to be experiencing pain and / or distress that cannot be promptly alleviated, it will be immediately removed from protocol and euthanatized by a staff veterinarian or veterinary technician.

Emergency Veterinary Medical Care: In the event of emergency, veterinary staff may be reached by pager or cellular telephone. Point of contact information is maintained in a directory.

Environmental Enrichment

Enrichment Strategy: During their acclimation period and up until the time of their experimental use, pigs will be individually housed but always kept in sight, sound and smell of their conspecifics. Enrichment items such as balls and Kong toys will be continually available to decrease stress and boredom. Nutritional enrichment may also be provided such as marshmallows, peanut butter and applesauce. Caretakers and veterinary staff will provide human interaction on a daily basis as part of routine husbandry requirements.

Enrichment Restriction: None

STUDY PERSONNEL QUALIFICATIONS AND TRAINING:

All investigators / research personnel involved in this study are trained and qualified to perform the specific procedures outlined in this protocol and have demonstrated an understanding of the humane care and use of research animals. In addition, they have taken part in discussions of pertinent laws and regulations concerning the use of animals in biomedical research. They are familiar with the concept of the 3R’s, including refinement, reduction and replacement, and have concluded that there is an absolute need for the use of animals in this study. They are familiar with the proper methods for minimizing and/or alleviating pain and/or distress in the animal species selected. They will either have a veterinary technician assigned to assist them who is trained and qualified to perform the techniques required for this study or have exhibited sufficient

proficiency themselves to justify unsupervised work without direct guidance from the veterinary staff. They have been advised on Institutional Animal Care and Use policy and are aware of the established reporting mechanisms for any observed deficiencies or concerns regarding animal use.

BIOHAZARD/SAFETY: All personnel participating in this protocol are currently enrolled in an Occupational Health and Safety Program, have received a risk assessment relative to protocol related hazards, and have been cleared to conduct all proposed activities listed. All personnel will be advised of the potential for zoonotic disease transmission. This is considered minimal risk as animals are procured from USDA-licensed vendors and are only used if determined to be healthy by the veterinary staff. There is potential for sharps injury from needles and surgical instruments. This risk will be minimized by using standard surgical techniques, sharps safety and standard precautions. There is potential for animal bites that will be reduced by socialization of animals prior to their experimental use and using standardized animal handling procedures as well as appropriate personal protective equipment (PPE). There is potential for exposure to waste anesthetic gases that will be minimized by using cuffed endotracheal tubes and an appropriate WAGS scavenging system.

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