Guidelines for Conducting Epidemiological Studies of Blast Injury

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Introduction

Blast injuries are often caused by more than one mechanism, do not occur in isolation, and typically elicit a secondary multisystem response. Research efforts often do not separate blast injuries caused by blast waves from those caused by blunt force trauma and other mechanisms. To add more complexity to elucidating blast injury pathophysiology, symptoms are often not immediately recognized or noticeable by a blast-exposed individual, especially when the individual is exposed to the blast waves but do not sustain blunt force trauma[1]. Currently, limited data and evidence-based guidelines exist regarding complex, multisystem injuries associated with blast exposure. Epidemiological studies are critical for obtaining the necessary data to understand the mechanisms of injury caused by explosions, the response of an individual to a blast event as well as long-term effects of blast exposure. Data elements required to evaluate an individual's response to blast exposure are summarized in Figure 1.

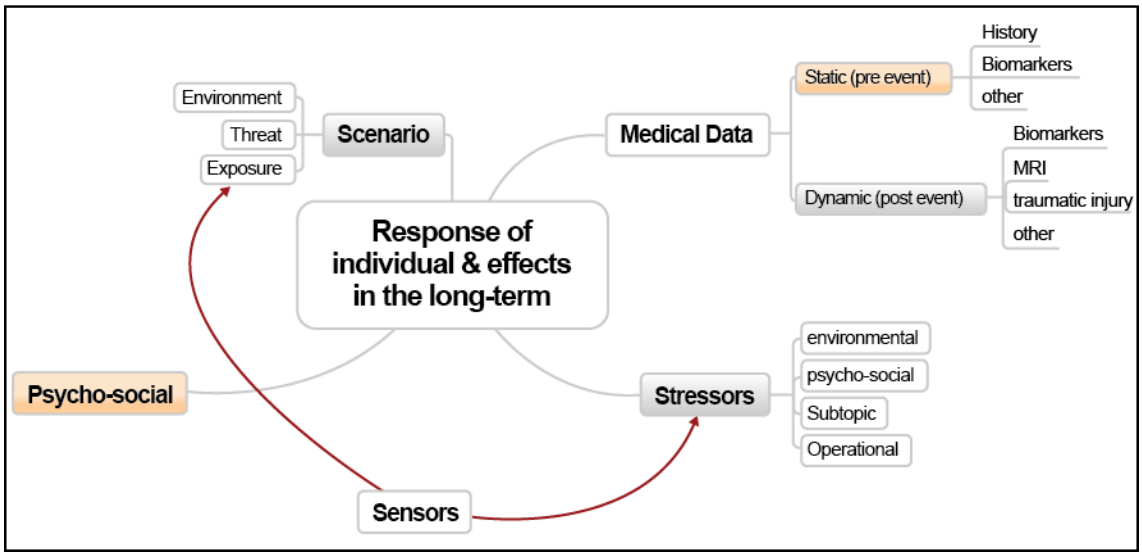

Figure 1. Data Elements Required to Understand the Response to Blast Injury[3]

15 experts from nine different NATO nations developed in the HFM Research Task Group (RTG; HFM-234 (RTG)) "Environmental Toxicology of Blast Exposures: Injury Metrics, Modeling, Methods and Standards" Guidelines for Conducting Epidemiological Studies of Blast Injury.[3] These guidelines are intended to provide blast injury researchers and clinicians with a basic set of recommendations for blast injury epidemiological study design and data collection that need to be considered and described when conducting prospective longitudinal studies of blast injury. The objectives of this document are:

a. To raise awareness with regards to the complexities and pitfalls of blast injury research
b. To standardize and promote good research practices
c. To help the community to generate valid and comparable results
d. To increase the quality of publications in this field of research

It is the intention of the HFM-234 (RTG) that these guidelines be used in concert with the companion comprehensive "Dictionary of Blast Injury Research Terms" developed by the NATO HFM-234 (RTG).[3]

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Requirements for Conducting a Blast Injury Epidemiological Study

A well-designed blast injury epidemiologic study should include an exposure assessment, an exposed population, and an unexposed population. Accurate blast exposure information is critical as this information is made part of the study and is used to determine health outcomes.[4] The framework requirements for conducting a blast injury epidemiologic study are similar to those found in Institute of Medicine (IOM) studies[2] and other well documented epidemiological protocols.

Prospective Longitudinal Studies for Blast Injury – Study Design

A prospective, longitudinal epidemiologic study is often the best non-experimental means to confirm and quantify associations between exposure factors and health outcomes, although rigorous planning, coordination, and cost factors must be considered. The ultimate goal of conducting blast injury studies is to elucidate the physical, biological, and psycho-social mechanisms that cause blast injuries so that control measures can be implemented to prevent or reduce additional illness. A study needs to examine to some extent the progress and development of a potential disease or pathological factor or the response to blast.[5]

Alternatively, a retrospective study (e.g., observational or phenomenological) involving data analysis based on medical history documentation can be used to identify certain components of importance if a full set of well-defined data exists for a focused hypothesis. However, researchers often still need to conduct a prospective study to control for variability in the study population, data collection protocols, and data elements of interest to which registry data may not be focused. Accurate blast exposure information is critical this information is made part of the study and is used to determine health outcomes[4]. Efforts should be made to make the response to blast exposure as specific as possible.

Framework Elements - Recommendations/Advantages

The framework requirements for conducting a blast injury study are similar to those found in IOM studies and other well-documented epidemiological protocols. Following elements describe the required framework to conduct an epidemiological study and the specific requirements for executing a blast injury study.[6]

- Well-Defined Research Question
- Focused Hypothesis
- Well-Defined Research Plan
- Sampling Methods
- Identifying Biases and Study Limitations
- Data Analysis Plan: Defining All Variables and Sample Size Requirements
- Documenting Survey Instruments and Operational Procedures
- Other Potential Considerations:
    - Analysis Phase

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- Banking of Biological Specimens
- Interdisciplinary Approach
- Quality Assurance
- Ethics

Study Population and Sampling Methods

The choice of the study population, including both the exposed and the control (i.e., unexposed) groups is a key factor in the design of a longitudinal study. The choice of study population affects not only operational aspects such as cost, administration, and field operations, but also generalizability and overall impact of results. Further, the designation of the study population may lend itself to the choice of the control group, but the choice of the control group also has major ramifications on the aforementioned operational and impact aspects.[7]

Blast Injury Data Collection

To determine and understand the etiology associated with blast exposure, researchers should collect both initial exposure data, as well as data related to linking biological health outcomes to blast exposure.

Parameters of Interest to Track Initial Exposure to Blasts (Table 1)

Three broad categories have been identified as parameters of interest to track initial exposure to blast:

- Characterizing the threat itself, including the type and size of explosive, the exposure environment, and the distance and orientation of the service member from the threat
- Capturing information related to the individual affected by the threat as well as the scenario (e.g., air sentry partly exposed, dismounted personnel kneeling down behind wall, etc.)
- Capturing exposure measurements related to the threat

Detailed information regarding the types of data required to track the initial exposure is discussed below and summarized in Figure 1 for quick reference.

Table 1. Parameters of Interest to Track Initial Exposure to Blasts

Category	Parameter
Threat	• Characterize the threat in terms of its family (e.g., type of IED, mine), charge estimate, type of explosive (pure charge versus mixture of components), road and soil conditions, apparent crater dimensions, detonation method, etc. • Characterize the threat environment (e.g., altitude, open air, explosion within or behind structures, ambient temperature) • Estimate (measure) the distance between the warfighter and the threat as well as the body orientation

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Category	Parameter
Individual	• Determine key demographics of individual (e.g., ID, sex, age, weight), relevant medical history (e.g., previous injuries), personality traits, Service (Army, Air Force, Marines, Navy, etc.), artillery or infantry or occupation • Determine body posture and extent of body exposure to threat • Determine type of PPE worn as well as the size (form and function) • Assess for the presence of blunt impact and acceleration/deceleration, including linear and angular acceleration/deceleration of the entire body or body part, and contact pressure. In addition to the acceleration/deceleration data, these measurements should provide information on risks for skull fracture and brain injury • Identify all types of injuries, medical conditions and relevant physiological status (e.g. dehydration, fatigue/exhaustion), and their effects on the body, including clinical, paraclinical, and biological. An indication of the injury data collection timeline must also be provided
Scenario	• Type of operational (e.g., training, maneuvers, other) • Estimate body posture and extent of body exposure to threat • Identify vehicle crew seating positions and order of march for dismounted troops • Define the event timeline and location
Measurements	• Identify the sensor system used (i.e., the specifications and capabilities of the sensor) • Describe the configuration of the suite of multiple sensors used (e.g., location and orientation of sensors with respect to a body coordinate system: aligned along 360 degrees) • Determine relationship of pressure sensor to exposure source (distance is directly related to amplitude) • Characterize the side on (static and dynamic), which includes face on pressures (amplitude and duration) of the blast

In addition, researchers should determine the relationship of a pressure sensor to the exposure source. There is an increased emphasis on the need to characterize the side on and face on pressures (both amplitude and duration) of the blast. The shape and impulse of the pressure from a blast is a measure of the energy that can be transported. The first blast wave from an explosion is the only thing that can be measured in a defined way. If the wave is reflected, the origin of the blast really needs to be determined. Accurate measurements are not needed for high explosives that are lethal. For blasts in the 60-120 kPa range, small increases in amplitude can mean the difference between no injury and injury. Knowing the amplitude and duration of a blast wave is crucial to determine its effect on the body. Furthermore, the distance from the blast is directly related to amplitude of the wave. Overall, the ability to accurately measure the intensity of blast waves in the 60-120 kPa range is needed to obtain quality correlations with the injury.

Data Required to Link Biological Health Outcomes to Blast Exposure

Data linking biological outcomes to blast exposure must be captured in order to determine the response of an individual to a blast event, as well as determine what influences that response. To collect these data, researchers should build a predictive system that includes signal analysis and pattern recognition. Data should be captured on both the threat and the surrounding environment.

A chart showing linkages among the various categories of data that need to be collected in association with a blast event was previously presented in Figure 1, while key categories of data required to link biological outcome to blast exposure and whether or not these categories represent data that are intrinsically dynamic or static (or both) are summarized below in 2.

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Table 2. Data Needed to Link Biological Health Outcomes to Blast Exposure

Category	Type
1. Environment	Dynamic
2. Threat	Dynamic
3. Stressors (environmental, operational, psychosocial)	Dynamic
4. Medical data (static and dynamic) • Link medical data with incident data (includes data from trauma registries, medical records, and other sources) • Data collected at event • Previous concussions (e.g., car accidents, sports)	Static and Dynamic
5. Psychosocial factors	Static
6. Personality traits of the individual	Static
7. Training and job history of the individual	Static
8. Identification of the cause of injury	N/A

Blast Injury Data Management

Whether a prospective longitudinal study is implemented or a minimum set of data specifications is agreed upon for data sharing between blast injury registries, guidelines for optimizing existing databases can be implemented to standardize the quality and content of these databases.

Existing databases which function as blast registries were developed to meet government and other regulatory functions specific to that nation or organization. Databases such as the Casualty Protective Equipment Analysis, and the Joint Theatre Trauma Registry, as well as data collected with forms like the Military Acute Concussion Evaluation (MACE)[8], or data collected by existing programs such as the Joint Trauma Analysis and Prevention of Injury in Combat (JTAPIC) may provide additional resources for researches in blast injury to conduct studies. Data in these existing sources range from mental health and personality traits, to exposure and injury or casualty information.

Designate a Data Manager

Epidemiological studies and registries often involve multiple individuals gathering data at multiple sites. Therefore, data management is an important issue. The integrity of the data must be maintained and ensured by a qualified data manager, either the PI or another individual to whom these responsibilities are assigned. The data manager will:

- Ensure adequate database specifications, security, structure, and functionality
- Prepare the data for the database (including, but not limited to ensuring adaptation of a protocol for de-identification of PHI)
- Assess data quality through periodic review and mitigate all data quality issues
- Assemble data for review and analysis

Discussion

Blast injury is a significant and complex problem facing military forces. The complexity of the injuries, particularly the multisystem response has made understanding blast injury etiology very

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challenging. In addition, limited blast injury data poses a significant challenge for researchers. Development of these guideline represents a significant step forward toward gathering the appropriate data to understand blast injury etiology and also highlights the value of facilitating a forum where multiple countries can share ideas and work together to solve an important health problem. To completely understand the nuances of blast injury etiology, continued multinational exchanges of scientific information will be crucial for improving health outcomes associated with blast injuries.

This document provides researchers with a solid epidemiologic framework and best practices to collect the appropriate data required to determine the response of an individual to blast exposure. These guidelines will benefit from their application and feedback to serve as a living guideline for future work in blast injury research. Although this document provides guidance on conducting blast injury epidemiologic studies to collect and manage blast injury data, there is still a need to have more detailed discussions on the toxicology of blast, particularly toxicological methods, and protocols relevant to understanding blast exposure effects. A concerted effort to bridge the fields of epidemiology and toxicology in a way that can impact and hopefully reduce burdens associated with blast injuries is imperative. Ultimately, to elucidate the biological mechanisms that cause blast injury pathophysiology, researchers need to have a solid toxicology framework as well. This framework needs to include at minimum, methods of understanding the dose, mechanism of the dosage and dose response endpoints of blast exposure (toxicology framework).

Lastly, these guidelines provide the minimum requirements to conduct a blast injury epidemiologic study and do not represent an exhaustive list. Some of the framework elements may differ by country. Thus, researchers admonished to follow guidance and adhere to rules and regulations provided by their respective nations.

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References

1. NATO Science and Technology Organization (NATO). (2011) *A Survey of Blast Injury across the Full Landscape of Military Science*. Retrieved from https://www.cso.nato.int/pubs/rdp.asp?RDP=RTO-MP-HFM-207

2. Institute of Medicine (IOM) of the National Academies. (2014). *Gulf War and Health, Volume 9: Long-term effects of blast exposures*. Washington, DC: National Academies Press. Retrieved from https://www.iom.edu/Reports/2014/Gulf-War-and-Health-Volume-9-Long-Term-Effects-of-Blast-Exposures.aspx

3. NATO Science and Technology Organization (NATO). (2013). *Environmental Toxicology of Blast Exposures: Injury Metrics, Modeling, Methods and Standards (HFM-234). Blast Injury Data Collection Guidelines*.

4. National Academy of Sciences. (2008). *A Review of Epidemiologic Studies of Veterans Exposed to Depleted Uranium: Feasibility and Design Issues*. Committee on Gulf War and Health: Updated Literature Review of Depleted Uranium. The National Academies Press. Retrieved from http://www.nap.edu/catalog/12200.html

5. Bhandari, M. et al. (2010). Research Questions, Hypotheses and Objectives. *Can J Surg*; 53(4): 278–281.

6. World Health Organization (WHO). (2000). *Monitoring Bathing Waters - A Practical Guide to the Design and Implementation of Assessments and Monitoring Programmes*. Edited by Jamie Bartram and Gareth Rees. Retrieved from http://www.who.int/water_sanitation_health/bathing/bathing3/en/

7. College Entrance Examination Board. (2004). *Observational Studies and Bias in Epidemiology*. Manuel Bayana, Chris Olsen. Retrieved from http://www.collegeboard.com/prod_downloads/yes/4297_MODULE_19.pdf

8. US Directive-Type Memorandum (DTM) 09-033 *Policy Guidance for Management of Concussion/Mild Traumatic Brain Injury in the Deployed Setting* (21 June 2010)

DOI til publisert versjon / DOI to published version: 10.1136/jramc-2018-000948