

Protocol

Hypoxemia in the first 24 hours after trauma – an observational study

Version 1.3

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General Information

Protocol Title:	Hypoxemia in the first 24 hours after trauma – an observational study
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Economy:	The project is initiated by Jacob Steinmetz from Department of Anaesthesia, Centre of Head and Orthopaedics, 6011 Rigshospitalet, and supported with funds from the Novo Nordisk Foundation and Lægeforeningens Forskningsfond.
Study information:	The study will be carried out in accordance with the protocol and the applicable laws in the field.
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Abbreviation

COPD	Chronic obstructive pulmonary disease
SpO ₂	Arterial oxygen saturation measured by pulse oximetry
ICU	Intensive care unit
LOS	Length of Stay

1. Introduction

1.1 Background and rationale

Trauma is one of the leading causes of death and disability on a global scale.¹ Advanced Trauma Life Support guidelines state serious concern with the appearance of hypoxemia after trauma, and consequently recommend that supplemental oxygen should be provided for all severely injured trauma patients to avoid hypoxemia in the initial phase.² Oxygen is a vital part of human physiology and must be delivered to all metabolically active cells in the body.³ When patients receive supplemental oxygen, a series of autoregulatory mechanisms happen to ensure optimal oxygen levels and prevent hypoxemia and hyperoxemia⁴ which can have different harmful effects.⁵ The lack of oxygen resulting in hypoxemia can potentially be a reversible cause of poor outcomes and in worst case death, hence supplemental oxygen is recommended for trauma patients, although the evidence is sparse.⁶

In other high-risk patient groups, such as surgical and chronic obstructive pulmonary disease (COPD) patients, Loft et al. monitored arterial oxygen saturation (SpO₂) continuously and found that cumulative duration of desaturations with SpO₂ < 85% was significantly associated with myocardial injury after both surgery and exacerbation of COPD.⁷ In stroke patients, Rowat et al. found a higher mortality in patients that experienced hypoxemia, but after adjusting for National Institute of Health Stroke Scale and age, this association was not significant. In the study, hypoxemia was found at all stages during admission.⁸ Using continuous monitoring for 48 hours Sun et al. found that hypoxemia was common and prolonged in patients recovering from noncardiac surgery. Furthermore, this study showed that 90% of hypoxemic episodes SpO₂ < 90% for at least one hour went undetected by standard spot checks, which were typically conducted at intervals of 4-6 hours.⁹

Trauma patients can also be characterized as high-risk patients due to their high mortality.¹⁰ The incidence of prehospital hypoxemia in traumatic brain injury patients has been studied, Stassen et al. found a prevalence of 37.9%,¹¹ and Chi et al. further discovered that prehospital hypoxemia was associated with higher mortality.¹² Evidence about the incidence of hypoxemia in trauma patients after admission to a hospital is not well established. There is reason to suspect that trauma patients can experience episodes of hypoxemia after admission and that the incidence of hypoxemia may differ between day and night as shown in several other patient populations.^{13,14,15} Potential incidences of severe hypoxemia, from patients being admitted to a trauma centre to subsequent care in a ward, should be avoided, since severe hypoxemia is associated with harmful effects.^{7,8} Hypoxemia can be detected and potentially corrected with more advanced measuring equipment.⁹ It is relevant to conduct a study with the purpose of determining the occurrence and distribution over the first 24 hours after hospital admission of hypoxemia by continuous SpO₂ monitoring in trauma patients, since this could potentially have important clinical implications and be useful in improving patient outcomes.

1.2 Study objectives and hypothesis

The aim of this study is to examine the occurrence and duration of episodes of hypoxemia in trauma patients in the first 24 hours after trauma and to compare their incidences during the day (08.00-19.59) and night (20.00-07.59).

We hypothesize that hypoxemic episodes will be more frequent during the night than during the day.

1.3 Study design

This study is a prospective, observational study. The protocol is structured according to the 2013 SPIRIT statement.

2. Methods

2.1 Study setting

This study is a single centre study of trauma patients at Rigshospitalet, Denmark. Rigshospitalet holds the only major trauma centre in the eastern part of Denmark, and every year around 1000 trauma patients are treated here.¹⁶ Patients are admitted from the Capital Region of Denmark with around 1.9 million inhabitants and the Region of Zealand with around 850.000 inhabitants.¹⁷

In the prehospital phase, the initial assessment of trauma patients will often be conducted by a prehospital physician specialized in anesthesiology/critical emergency medicine in Denmark. If patients are to be admitted to the trauma centre at Rigshospitalet, they are usually required to fulfil criteria based on either mechanism of injury or anatomical criteria.¹⁸ A primary, secondary and tertiary triage system is used to optimize patient treatment and ensure continuous monitoring of the patient. The primary triage occurs at the scene of injury. It is intended to assess the patient, identify life-threatening injuries and initiate appropriate interventions in accordance with the ABCDE-principals¹⁹. The secondary triage occurs at the trauma centre at a hospital, where there is more staffing and equipment available. Once at the trauma centre, a team consisting of a wide variety of medical professionals will meet the patient. Often in blunt trauma, patients will get an initial assessment and management followed by a full trauma CT scan depending on the severity and the nature of the patients' injuries. Depending on the findings in the clinical assessment and scan the patient will be admitted for further treatment either at a general ward, where surveillance is less thorough, intensive care unit (ICU) or alternatively directly to the operating room as a part of the tertiary triage.^{2,18}

The patients in this study will be included in the trauma bay at Rigshospitalet.

2.2 Participants

All patients with trauma team activation in the trauma bay at Rigshospitalet, including both direct transport and secondary transfers, will be screened for potential inclusion in the study. Patients will be included if they comply with the following eligibility criteria:

2.3 Inclusion criteria

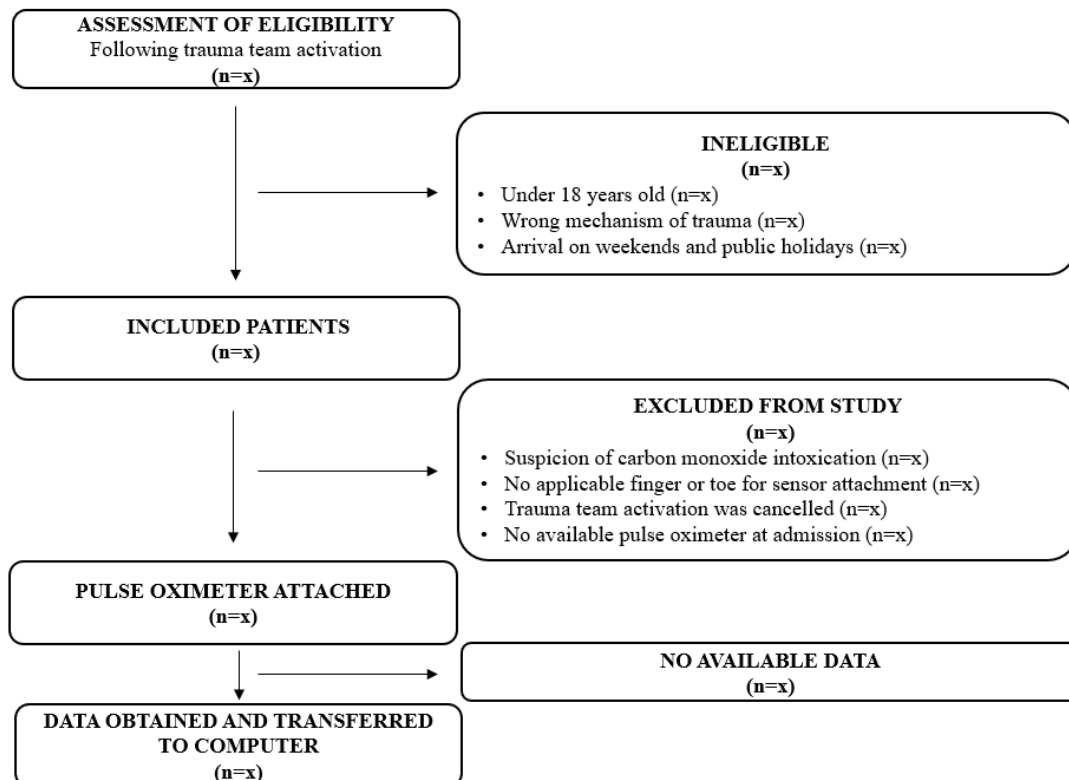
- Patients aged ≥ 18 years
- Blunt or penetrating mechanism of trauma
- Trauma team activation
- Admission to a ward/ICU from trauma centre

2.4 Exclusion criteria

- Patients with a suspicion of carbon monoxide intoxication
- No applicable finger or toe for sensor attachment
- Trauma team activation was cancelled
- No available pulse oximeter at admission

The expected process of patient inclusion and data collection is demonstrated in figure 1.

Figure 1: Flowchart describing patient inclusion and data collection process



2.5 Outcomes

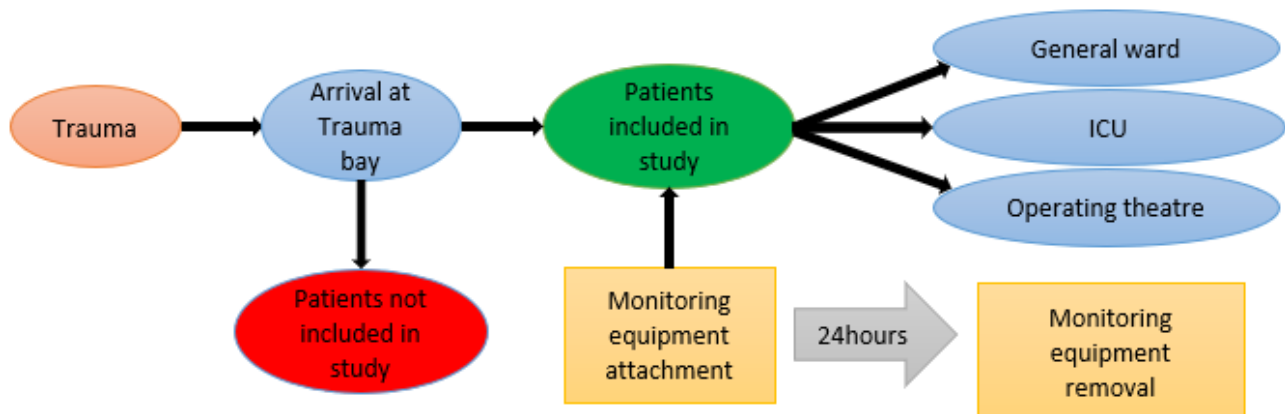
Primary outcome

- The occurrence and daily distribution of clinically relevant hypoxemic episodes defined as $\text{SpO}_2 < 90\%$ for > 5 minutes, within the first 24 hours after trauma

Secondary outcomes

- The occurrence of clinically relevant hypoxemic episodes $\text{SpO}_2 < 90\%$ > 5 minutes in different departments including trauma centre, ICU, general ward, operating theatre and recovery room.
- The occurrence of prolonged hypoxemic episodes $\text{SpO}_2 < 90\%$ for > 30 minutes per episode
- Cumulated time of hypoxaemia $\text{SpO}_2 < 90\%$

2.6 Participant timeline



2.7 Sample size

We estimate that 5% of patients during the day and 20% of patients during the night will experience hypoxemia defined as $\text{SpO}_2 < 90\%$ for > 5 minutes. A sample size calculation with an alpha of 5% and a power of 80% estimates a need of 150 study participants. Based on previous experience with continuous pulse oximetry it is expected that 10% will be excluded due to unsuccessful data collection. Therefore, the aim is to include 165 patients.

2.8 Recruitment

The trauma bay at Rigshospitalet will be equipped with the oximetry equipment, and measurement can be started as early as possible. At the trauma bay, a doctor will conduct the screening and inclusion of patients to the study at their arrival. After study inclusion, monitoring equipment will be attached by a nurse in the trauma bay. Subsequently a member of the study investigator group will obtain consent.

2.9 Data collection methods

Continuous pulse oximetry will be used to measure SpO_2 . SpO_2 , heart rate, pulse amplitude and alarm status will be measured every second during a 24-hour period on all study participants.

The Nellcor™ Portable SpO_2 Patient Monitoring System, PM10N (Medtronic, 15 Hampshire Street, Mansfield, MA 02048, USA) is used as monitoring device. The Covidien Nellcor FLEXMAX or a similar probe will be placed on the patients' index finger, alternatively another finger or toe. If there are no available extremities the patient will be excluded from the study.

If a patient has a peripheral venous catheter or a blood pressure cuff, the probe is placed on the other arm. The probe cable will be fastened with adhesive band across the back of the patient's hand, as an attempt to prevent untimely probe removal. The monitoring device will be placed in a telemetry bag with a soft fabric string which can be placed in the bed or around the patient's neck if awake. The data will be transferred and stored locally on a secure drive.

Since the study is observational, and we would like to identify episodes of hypoxemia that would go undetected under standard care, the alarm system on our monitoring device will be set restrictive. Alarm if $\text{SpO}_2 < 80\%$ or the heart rate is < 40 beats per minute or > 140 beats pr. minute.

Data collection will continue for up to 24 hours. If there is an untimely removal of the probe, the device will switch off, and data collection will stop at this point, unless the device is turned on again. After 24 hours of measurement, an investigator will collect the device and transfer the data by USB cable to a computer for secure storage and further analysis.

The following data will be obtained by accessing the study participants' medical records.

- Patient characteristics including name, unique patient identifier (civil registration number “CPR nummer”), age, sex, height and weight
- Pre-hospital circumstances including vital signs, Glasgow Coma Score (GCS), mechanism of injury, variables regarding airway management and oxygen treatment, use of sedatives and opioids, transportation mode to the trauma centre
- Vital signs at trauma centre arrival
- Clinical parameters during admission including vital signs, variables regarding airway management and oxygen treatment and use of sedatives and opioids
- Time points including date and time of trauma, trauma centre/ICU/ward/operating theatre/recovery room arrival and departure, time and duration of anaesthesia and surgery within first 24 hours
- Injury severity score (ISS) and abbreviated injury scale (AIS) scores
- Co-morbidities prior to trauma: Categorised in heart disease, lung disease and other diseases
- Hospital and ICU LOS
- Ischaemic events (myocardial infarction or cerebral ischemia)
- Specifics of possible brain injury (type and extent) and other cerebral complications
- 30-day mortality
- Active smoker (yes/no)

Patient data will be used to describe the population of study participants. This is of great importance, to make the results transferable to the relevant trauma patients.

Time points will be used to specify study participants' location at times of desaturation.

2.10 Data management

Personal data will be processed in the study, and we comply with both the Data Protection Act and the Data Protection Ordinance.

The Nellcor PM10N pulse oximeter will hold patient data for the observation time only. Following data transfer to a secure drive, all data will be cleared from the devices.

In the computer monitoring data will be stored as csv-files on a secure drive.

Patient data collected from the medical records are stored and managed using Research Electronic Data Capture (REDCap) an electronic data capture tool hosted at Rigshospitalet. This is a secure, web-based software platform designed to support data capture for research studies.²⁰

2.11 Statistics

To account for artefacts during the measurement period the method described by Haahr-Raunkjaer et al. is used. It is stated that artefacts are defined as SpO₂ values after a change in SpO₂ of more than 4% per second.²¹

Data with assumptions of normal distribution will be described with means and standard deviations, categorical data will be reported with numbers and percentages.

Data with assumption of being non-normally distributed will be reported with medians with interquartile ranges.

The student's t-test will be used for parametric data to compare the two study groups.

The Mann-Whitney-U-test will be used for non-parametric data to compare the two groups (day vs night).

A Kruskal-Wallis test will be used for non-parametric data when comparing the different hospital departments.

The modified Wald method will be used to determine the 95% confidence intervals.

A p-value of <0.05 will be considered statistically significant.

2.12 Project timeline

	Pre-study	Month 1-6	Month 7	Month 8
Preparation of protocol	x			
Ethical approval	x			
Protocol registration	x			
Data collection		x		
Data analysis		x		
Manuscript writing			x	
Publication				x

3. Ethics and dissemination

3.1 Risks and adverse events

The study is observational, without an intervention and non-invasive. Hence, we do not believe, that study participants will be exposed to any relevant risks of neither complications nor adverse events in relation to participating in the study.

3.2 Study ethics

As the nature of the study is exclusively observational, without an intervention, non-invasive and is conducted on humans, it is required to obtain approval at the Regional Research Ethics Committee in the Capital Region and the Capital region of Denmark data controllers register.

As described earlier we do not believe that study participants will be exposed to any additional risks of complications or adverse events. Hence the study is minimally demanding for participants. On the contrary, participation in the study will provide us with important knowledge in monitoring and treating trauma patients, improving the overall outcomes for future trauma patients.

The restrictive setting of the alarm system on the pulse oximeter is necessary to capture an accurate representation of all episodes of hypoxemia that might otherwise go undetected with standard care that does not measure continuously. The restrictive alarm setting on the pulse oximeter does not impact the standard measuring equipment used in patient care.

3.3 Consent

To make studies with the goal of improving the monitoring and treatment of traumatic injuries, it is necessary to include unconscious and incompetent study participants, as no clinically relevant animal model exists.

Hence, we consider all trauma patients to be without ability to consent to participation.

The study participants eligible for this study are considered incompetent and unable to consent because of their acute and potentially life-threatening injuries.

Patients will be eligible at the trauma bay of Rigshospitalet, and it is important to include participants as early after admission as possible. Hence, there is a need to use the emergency research consent procedures.

In accordance with §11 and §19 in the Scientific Ethical Committees Act (LBK nr. 1338 from September 1., 2020), the act can allow acute studies without prior consent if some criteria are met. Subsequently, the investigators must seek informed consent from study participants or proxy consent.²²

Consent will be sought from the study participant's next of kin and a designated independent clinician as soon as practically possible, and when/if possible, from the study participant themselves. If the study participant is not able to consent or dies within 30 days, consent from the next of kin and the designated independent clinician will be accepted as the final consent. If it is not possible to identify or contact any next of kin after multiple repeated attempts, consent from the designated independent clinician will stand alone. An agreement to act as independent clinician will be made with an impartial doctor in Rigshospitalet. The independent clinician will have access to the study protocol and the written study participant information.

The consent process is described in more detail below. Investigators will seek informed consent from a designated independent clinician and the study participant's next of kin in an undisturbed environment as soon as possible after admission. Information regarding the study will be relayed in both a verbal and written manner in undisturbed circumstances. Before continuing the conversation, the next of kin will be made aware of their right to have an advocate/supporter by their side. If this

requires extra time, the necessary time will be given. Study participants' next of kin are being informed about their right to have a 24-hour consideration period between being informed about the study and giving their consent.

During the study participant's hospital stay, there will be an ongoing evaluation by study investigators on whether the participant becomes capable of consenting themselves. When/if this is the case, consent will be sought as soon as possible. Information regarding this study will be relayed in both a verbal and written manner in undisturbed circumstances.

The study participant will be made aware of their right to have an advocate/supporter by their side, before continuing the conversation. If this requires extra time, the necessary time will be given. Study participants are informed about their right to have a 24-hour consideration period between being informed about the study and giving consent.

Inclusion of the patient in the study will remain until a decision about consent has been reached by either the patient themselves or the next of kin and designated independent clinician .

Written and verbal study information will be given by trained personnel from the research team. The same research team members will obtain informed consent forms.

It will be made clear in both written and verbal manner that participation is voluntary and can be withdrawn at any time without affecting the current or future treatment of the study participant. It will also be made clear that the informed/proxy consent contains permission for the personnel involved in the study to gather information from the study participant's medical record.

According to the standard informed consent form from the National Ethics Committee regarding competent participants, the participant can choose to be informed about secondary findings due to their treatment at the hospital. However, the purpose of this study is not to generate new knowledge about a specific participant, so we find that this question is redundant, and have omitted the question from the consent form to spare the participant from making unnecessary decisions.

3.4 Confidentiality

All health care professionals are subject to confidentiality regarding patient information. Danish Safety Patient Authority ensures this right on behalf of patients and study participants. Patient specific data is relied on the medical record system. REDCap will hold relevant study participant data as stated above in the protocol. All relevant documentation regarding investigators can be found in the study master file.

3.5 Assurance

Study participants will be covered by the Danish Patient Compensation (Patienterstatningen).

3.6 Economy

The project has been initiated by Jacob Steinmetz from Department of Anaesthesia, Centre of Head and Orthopaedics 6011, Rigshospitalet.

The project received 120.000 DKK in funding from Lægeforeningens Forskningsfond, which covers most of the salary for a research year student. Additionally, 26.730 DKK from The Novo Nordisk Foundation covering the remainder of the salary of a research year student and the purchase of project equipment. The funding has been allocated to a research account within the

Department of Anaesthesia, Centre of Head and Orthopaedics 6011, Rigshospitalet.
There are no conflicts of interests.

3.7 Declaration of conflict of interests

None

3.8 Access to data

All project investigators will have access to data regarding study participants.

3.9 Protocol amendment on April 11th 2024

Since February 20th 2024 the project only included patients on weekdays, but later in April, patients will be included 24/7 seven days a week. The clinical relevance of hypoxaemia in trauma patients is relevant for ALL trauma patients, regardless of timing of the admission. As the primary outcome is assessment of hypoxaemia in daylight hours versus night time all types of trauma patients are relevant to assess, and we assume that patient groups will be comparable without considerable bias between those two periods (weekdays/weekend). However, we will perform an analysis of whether included patients are comparable in day vs. night time in demographic data, e.g. age, sex, trauma mechanism and more.

3.10 Dissemination

A protocol registration at ClinicalTrials.gov will be made after protocol approval.

When informed consent is given, participants can indicate whether they want the study results after the study has been finished. In that case, they will have a summary of the overall the results sent to them after the study has concluded.

The results of this study will be relayed at www.clinicaltrials.gov. Additionally, they will be published in a relevant peer-reviewed journal and/or presented at an international conference irrespective of whether the results are positive, negative, or inconclusive.

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