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ABSTRACT

Introduction Perioperative haemodynamic instability is associated with postoperative morbidity and mortality. Macrocirculatory parameters, such as arterial blood pressure and cardiac output are associated with poor outcome but may be uncoupled from the microcirculation during sepsis and hypovolaemia and may not be optimal resuscitation parameters. The peripheral perfusion index (PPI) is derived from the pulse oximetry signal. Reduced peripheral perfusion is associated with morbidity in critically ill patients and in patients following acute surgery. We hypothesise that a low intraoperative PPI is independently associated with postoperative complications and mortality.

Methods and analysis We plan to conduct a retrospective cohort study in approximately 2300 patients, who underwent acute non-cardiac surgery (1 November 2017 to 31 October 2018) at two Danish University Hospitals. Data will be collected from patient records including patient demographics, comorbidity and intraoperative haemodynamic values with PPI as the primary exposure variable, and postoperative complications and mortality within 30 and 90 days as outcome variables. We primarily assess association between PPI and outcome in multivariate regression models. Second, the predictive value of PPI for outcome, using area under the receiver operating characteristics curve is assessed.

Ethics and dissemination Data will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology and results published in a peer-reviewed journal. The study is approved by the regional research ethics committee, storage and management of data has been approved by the Regional Data Protection Agency, and access to medical records is approved by the hospital board of directors (ClinicalTrials.gov registration no: NCT03757442).

Strengths and limitations of this study

- Inherent to the nature of the retrospective cohort study design, we describe association not causation.
- While we perform retrospective analysis, clinical data are prospectively collected.
- We obtain clinical database registration and peer review publication of objectives, outcomes and statistical analysis plan attempting to minimise the bias inherent to the retrospective study design.
- To the best of our knowledge, no larger cohort study describing association between PPI and postoperative outcome exists, and findings may promote clinical applicability in emergency surgery.

INTRODUCTION

Background

Perioperative haemodynamic instability is associated with postoperative morbidity and mortality. Patients undergoing acute major abdominal or hip fracture surgery have high complication rates and account for a major part of overall postoperative mortality in developed countries.[1 2] These patients are often frail, with multiple comorbidities making them susceptible to the effects of anaesthesia and surgery.[3–5] Despite the benefit of a multidisciplinary effort to improve perioperative care, such patients demonstrate a high risk of complications and death.[6–9] Conventional perioperative haemodynamic monitoring is often based mainly on heart rate (HR) and mean blood pressure (MAP).[10] Although perioperative hypotension is associated with complications in major surgery, blood pressure is often an inadequate marker of perioperative

organ perfusion, confounding the administration of fluid and vasoactive medications.[11] Minimally invasive haemodynamic monitoring of cardiac output (CO), and goal-directed therapy based on stroke volume optimisation, has been associated with improved outcome in major elective surgery, but high-quality evidence for the advantage of such monitoring in emergency surgery is sparse.[12 13]

Macrocirculatory parameters such as MAP and CO may be uncoupled from the microcirculation during sepsis and severe blood loss due to sympathetic or medically induced vasoconstriction, and as such, these parameters are not necessarily ideal for directing resuscitation.[14–16]

Assuming that blood flow is directed from peripheral tissue to vital organs during progressive stages of circulatory impairment and shock, a non-invasive method to detect impaired peripheral perfusion could be a relevant endpoint to identify haemodynamic instability.[17]

The peripheral perfusion index (PPI) has the advantage that it is derived from the photoelectric plethysmographic pulse oximetry signal most likely obtained in all patients for the evaluation of arterial oxygen saturation (SAT) already in the emergency room and continued during and after surgery as in wards and in the intensive care unit (ICU). The PPI reflects the ratio between the pulsatile and non-pulsatile component of the arterial waveform as assessed by light traversing the tissue addressed, most often the finger, and it decreases in response to hypoperfusion.[18] Thus, PPI reflects changes in peripheral perfusion and blood volume[19 20] and reduced peripheral perfusion is associated with morbidity following acute surgery[21] in critically ill patients and in patients presenting septic shock.[22 23] However, it remains uncertain which threshold for PPI should trigger intervention in patients undergoing acute surgery reflecting that evaluation is made only in relatively small populations of mixed medical and surgical patients.

Hypothesis

We hypothesise that PPI reflects impaired peripheral circulation and that patients with low intraoperative PPI, independent of MAP, have higher risk of postoperative complications and mortality than patients with normal or high PPI.

Objectives

The main objective of this study is to evaluate the association between intraoperative PPI and outcome defined as severe postoperative complications and 30 and 90 days of mortality. Second, we assess the predictive value of intraoperative PPI in relation to outcome and evaluate whether PPI demonstrates better prediction of adverse outcome than the commonly used MAP thresholds and try to establish intervention thresholds for PPI in acute high-risk non-cardiac surgical patients.

METHODS

Study design

In an observational retrospective cohort study design of patients who underwent acute major abdominal or hip fracture surgery from 1 November 2017 to 31 October 2018 at Hvidovre and Bispebjerg University Hospitals, Copenhagen, Denmark, we will conduct retrospective analysis of prospectively collected clinical data, that is, collecting data after defining exposure and outcome variables and plan for the statistical analysis.

Participants

We will include patients ≥18 years identified by civil registration number, a unique identifier assigned to all citizens at birth, from the hospital's electronic medical records via specific procedural codes specifying the acute orthopaedic or abdominal surgery that the patient is exposed to during the period of interest, thereby including approximately 1000 patients who undergo acute hip fracture surgery and 1300 acute abdominal surgery.

Inclusion criteria

- Orthopaedic surgery patients with fracture of the hip booked for or having performed procedures with the following procedural codes: KNFB02, KNFJ81, KNFJ51, KNFJ52, KNFJ70 representing arthroplasty, intramedullar nailing and screws, respectively.
- For abdominal surgery patients, we include patients booked for acute laparoscopy for diagnostic purposes (KJAH01) and explorative laparotomy (KJAH00). To identify all patients having performed acute abdominal surgery, we also include surgery related to ileus: KJFK00, KJFK01, KJFK10, KJAP00, KJAP01, KJFK96, KJFK97, any perforation of vicera: KJDA60, KJDA70, KJDA80 and any ischaemic condition of the gut: KJFB00, KJFB01, KJFB33, KJFB34, KJFB96, KJFB97.

Exclusion criteria

- No sampling of PPI registered.
- Foreign/temporary civil registration number that prevents follow-up.
- Earlier enrolment in the cohort.

Data collection

Data will be collected from patient records and anaesthesia charts and recorded and managed using REDCap (Research Electronic Data Capture) hosted by The Capital Region of Denmark. REDCap is a secured, web-based application designed to support data acquisition by providing (1) an intuitive interface for validated data entry, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data download to common statistical packages and (4) procedures for importing data from external sources. Data entry will be by the main author (MA) and a research assistant (ANWT). If questions arise, the final decision on data entry will be by the senior author (NBF). As registered at ClinicalTrials.gov, data collection initiated on 1 February 2019 is expecting completion on 1

Table 1 Intraoperative variables

Variable	Sampling time	Data source
Peripheral perfusion index*	Absolute values every 15th minute and lowest 1 and 5 min averaged values from the induction of anaesthesia through surgery	Electronic anaesthesia chart
Mean arterial pressure	Absolute values every 15th minute and lowest 1 and 5 min averaged values from the induction of anaesthesia through surgery	Electronic anaesthesia chart
Heart rate	Absolute values every 15th minute and lowest 1 and 5 min averaged values from the induction of anaesthesia through surgery	Electronic anaesthesia chart
Arterial saturation	Absolute values every 15th minute from the induction of anaesthesia through surgery	Electronic anaesthesia chart
Temperature	Absolute values every 15th minute from the induction of anaesthesia through surgery	Electronic anaesthesia chart
Vasoactive medications: ephedrine, phenylephrine, dopamine, dobutamine, epinephrine and norepinephrine	Cumulative amounts in operating theatre	Electronic anaesthesia chart
Anaesthetic methods: epidural anaesthesia, spinal anaesthesia, combined epidural and spinal anaesthesia, sedation, general anaesthesia		Electronic anaesthesia chart
Total intravenous anaesthesia or anaesthesia with volatile anaesthetics		
Total fluid administered	Cumulative amounts in operating theatre	Electronic anaesthesia chart
Haemoglobin	Any values measured perioperatively	Electronic patient record
Serum lactate	Highest perioperative value	Electronic patient record
Total operation time	Minutes	Electronic patient record

*Primary exposure variable.

November 2019. Overall study completion is expected to be on 1 October 2020.

Exposure variables

According to clinical routine, the staff measured MAP, HR, SAT, temperature (Tp) and PPI, which is captured by the pulse oximeter. Data were obtained continuously from the patient monitors (Philips IntelliVue MP50; Koninklijke Philips, The Netherlands) and automatically exported to the electronic anaesthesia chart. Blood pressure was measured using the oscillometric non-invasive technique or via radial arterial cannulation using pulse contour analysis. The latter will be obtained when available. We will record PPI, MAP, HR, SAT and Tp intraoperatively, defined as the period from the induction of anaesthesia to last suture by reviewing the anaesthesia chart. Data will be collected as 15 min averages and lowest 1 and 5 min averaged values for PPI, MAP and HR.

In the intraoperative anaesthesia charts in our institutions (EPIC), haemodynamic variables are presented as columns of averages, generated on a time interval. Data are lifted sequentially as different time intervals which is not the same as an analysis of rolling averages.

For the assessment of association between combinations of high/low MAP and high/low PPI, we define pragmatic thresholds for extremely low and low PPI and MAP to be 0.5 and 1.5 and 65 mm Hg, respectively (table 1).[19 24 25] We consider PPI to be the primary exposure variable.

Outcome measures

Outcome will be graded according to the Clavien-Dindo classification of surgical complications[26] and severe complications will be defined as complications grade III to V, that is, requiring surgical, endoscopic or radiological intervention and life-threatening complications requiring ICU management or death. All-cause mortality at postoperative days 30 and 90 will be obtained by review of the patient records (table 2). The primary outcome is any severe complication or death within 30 days.

Other exposures

Basic patient demographics (ie, age, sex, height, weight) and comorbidity will be obtained from the patient record (table 3). Comorbidity will be ranked according to (1) American Society of Anesthesiology (ASA) that indicates physical health to predict postoperative morbidity: 0 (lowest risk) to 5 (highest risk)[27]; (2) WHO/Eastern Cooperative Oncology Group/Zubrod score that assesses the patient's ability to carry out daily activity: 0 (unrestricted) to 4 (bedridden)[28]; (3) the Charlson Comorbidity score[29 30] that categorises comorbidity based on International Classification of Diseases diagnosis codes.

Table 2 Outcome variables

Variable	Sampling time	Data source
30-day mortality*	All cause, within 30 days from surgery	Electronic patient record
90-day mortality	All cause, within 90 days from surgery	Electronic patient record
Postoperative complications†	Events occurring until hospital discharge	Electronic patient record
Total length of stay	In days	Electronic patient record
Readmissions	Number including reasons	Electronic patient record

*Primary outcome variable.
†Postoperative complications will be ranked according to Clavien-Dindo classification.

In addition, we will collect information on type of surgery, anaesthetic method, use of vasoactive medication and intravenous-administered resuscitation fluids.

Statistical analysis

Categorical variables will be presented as count (frequency) and continuous variables as mean±SD if normally distributed and as median (25th–75th percentile) if skewed. A two-sided p-value <0.05 will be considered statistically significant.

Distribution of data will be graphically presented and inspected using Q–Q and box plots and tested with the Kolmogorov-Smirnov and the Shapiro-Wilk tests. Variability will be assessed using box plots. If necessary, data will be logarithmically transformed to account for skewness and changes in variance. Descriptive statistics will be applied and differences between groups analysed using the χ^2 test, Fisher's exact test or univariate logistic regression as appropriate.

Cross-tabulation and univariable logistic regression models will be applied to test combinations of exposure variables and outcome assessing potential interaction and confounding factors. Univariable logistic regression models will be performed for PPI as the continuous non-dependent variable and dichotomous outcome as the dependent variable. Exposure variables with a significant association to outcome in univariable analysis will be included in a multivariable logistic regression model. Associations will be reported as ORs.

Table 3 Clinical history

Variable	Sampling time	Data source
ASA*	On admission	Electronic patient record
WHO/ECOG/Zubrod score**	On admission	Electronic patient record
The Charlson Comorbidity score	On admission	Electronic patient record

*ASA, American Society of Anesthesiology; **ECOG, Eastern Cooperative Oncology Group; ***WHO, World Health Organization.

The estimated probability of any severe complication or death within 30 days for high-risk acute abdominal or hip fracture surgery is approximately 45% and 30% in our setting, respectively.[8 31 32] A reasonable estimation of overall severe postoperative complications or death within 30 days is pragmatically set at 40%. We expect to include around 2300 patients in the cohort with approximately equal distribution between class of surgery. We plan to perform logistic regression models evaluating the association between the primary outcome and PPI. Using Whittemore's formula[33] requiring a dichotomous dependent variable and continuous risk factors, a sample size of 2300 patients with an event rate of 40% will enable us to detect an OR of 0.9 using a two-tailed test with a significance level of 5% and a power of 80%.

To evaluate the predictive value of a low (≤1.5) and extremely low (≤0.5) PPI in patients with an MAP ≥65 mm Hg (normotensive) and <65 mm Hg (hypotensive), association between combinations of normal/low MAP and PPI, we plan to perform multivariate logistic regression with dichotomisation of MAP and categorisation of PPI as described.

We plan to assess the predictive ability of PPI using the area (AUC) under the receiver operating characteristics curve. The multivariable model will be performed with and without PPI evaluating whether PPI increases or decreases AUC and the predictive value of the model. Graphically, presentation of the distribution of PPI stratified by postoperative complications and mortality will guide the estimation of cut-off limits for acceptable values when estimating sensitivity, specificity and predictive values. Subgroup analysis for type of surgery and anaesthetic method will be performed.

To evaluate the goodness-of-fit for each model and evaluate the observed versus expected outcome, we will draw calibration plots and apply the Hosmer-Lemeshow test.[34] If the AUC for the multivariable model including PPI >7 corresponding to sufficient predictive accuracy, we will apply non-parametric bootstrapping for internal validation by assessing the models for overfitting. The method applies unrestricted random sampling to draw observations from the original data set, thereby producing a total of 10 000 new data sets to which statistical analysis can be applied, limiting the risk of model overfitting. For each model, the median AUC from the 10 000 produced data set will be compared with the AUC of the original data set.

We plan to handle missing data on exposure variables exceeding 10%, by multiple imputation. If a large fraction of data is imputed, we wish to compare observed and imputed values. If missing data on outcome variables exceeds 10%, we plan to manually impute worst/best case scenarios and perform subgroup analysis.

Analysis will be by statistical software from RStudio (2016), Integrated Development for R. (RStudio, Boston, Massachusetts, USA) or SAS (V.9.4; SAS Institute, Cary, North Carolina, USA).

PATIENT AND PUBLIC INVOLVEMENT STATEMENT

Due to the fact that all data will be retrieved from medical records and anaesthesia charts without any impact on future treatment for the involved patients, we did not involve patients or the public in designing this study or writing the protocol.

ETHICS AND DISSEMINATION

The study is approved by the regional research ethics committee (H-18058705) and registered at Clinical.Trials.gov (NCT03757442). Access to hospital medical records was approved by the board of directors at the involved hospitals and departments. The storage and management of data are approved by the Regional Data Protection Agency (WZ 18049692 and WZ 17038300-1018-77).

The study adheres to the Declaration of Helsinki. No patient will be exposed to any inconvenience in relation to this study because all data are obtained retrospectively. Special identification numbers will be assigned to the working group obtaining data from the electronic patient records, logging entry and all data will be anonymous according to law.

Results will be published in a peer-reviewed journal and reporting will be according to the Strengthening the Reporting of Observational Studies in Epidemiology[35] and the Standards for Reporting of Diagnostic Accuracy Studies statements.[36]

LIMITATIONS AND BIAS

Patients will be identified in the hospital's electronic medical records via specific procedural codes for the acute orthopaedic or abdominal surgery in the specified period, which depends on whether eligible patients are registered correctly. For constructing the database, data will be transferred manually from the electronic patient record and the electronic anaesthesia chart, which leaves the risk of typing errors. Also, some variables, including medical history, are to be evaluated and transformed to scores/numeric values, but the database will be constructed with thorough description of variables to minimise bias. Intraoperative variables are obtained electronically and transferred manually to the database, which entails risk of typing errors but also holds the possibility of identifying artefactual data.

Double entry of data will not be logistically possible. The same person entering haemodynamic variables from the anaesthesia chart to the database will be reviewing the medical chart and categorising postoperative complications according to Clavien-Dindo classification. However, we argue that due to the nature of the Clavien-Dindo classification, which is a severity grading system based on treatment registered in the medical chart and not on symptoms that might be more susceptible for interpretation, the risk of bias is reduced. A formal, standardised definition of occurrence of perioperative complications like the StEP-COMPAC[37] recommends the Clavien-Dindo classification to assess composite morbidity scales alongside other measures of patient comfort to support benchmarking and meta-analysis of trials. We plan to thoroughly discuss the advantages and disadvantages, including the risk of differing interpretation by data collectors and hence bias and the possible limitation in comparing the results of this study with others assessing similar endpoints.

Data entry personnel will obtain data on both orthopaedic and abdominal surgery patients from both hospitals supposedly minimising the risk of systematic bias. Whenever questions arise, there will be conference between data entry personnel.

The relevance of recording intraoperative PPI is yet to be assessed in different categories of patients and we expect PPI to vary according to the general state of the overall circulation that may depend on, for example, age, comorbidity and health. Also, methods of anaesthesia may affect PPI and we suspect PPI to vary between subjects undergoing general anaesthesia, neuraxial anaesthesia and sedation as these methods have different effects on the autonomic nervous system and regulation of blood flow.

Evaluation of PPI has found a right skewed distribution with large variability which will be addressed when analysing the data.[19] Data will be collected and entered in the database prospectively, that is, after registration of primary and secondary endpoints at ClinicalTrials.gov and preferable after peer review of the protocol, minimising bias arising from the nature of a cohort study.

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Contributors MA, HS, CSM, SW and NBF participated in the study concept and design. MA and ANWT will conduct the construction of the database and data entry. MA, HS, JH, CSM, NHS, SW and NBF will participate in the study conduct, data analysis and writing of the manuscript. All authors will read and approve the final protocol manuscript. All above will follow the Vancouver principles to be granted authorship.

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Competing interests CSM: As head of research, the department receives direct and indirect research funding from Boehringer Ingelheim; Ferring Pharmaceuticals; and Merck, Sharp and Dohme, outside submitted work.

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