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Bedside hyperspectral imaging for the evaluation of microcirculatory alterations in perioperative intensive care medicine: a study protocol for an observational clinical pilot study (HySpI-ICU)

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ABSTRACT

Introduction Normalisation of macrocirculatory parameters during resuscitation therapy does not guarantee the restoration of microcirculatory perfusion in critical illness due to haemodynamic incoherence. Persistent microcirculatory abnormalities are associated with severity of organ dysfunction and mandate the development of bedside microcirculatory monitoring. A novel hyperspectral imaging (HSI) system can visualise changes in skin perfusion, oxygenation and water content at the bedside. We aim to evaluate the effectiveness of HSI for bedside monitoring of skin microcirculation and the association of HSI parameters with organ dysfunction in patients with sepsis and major abdominal surgery.

Methods and analysis Three independent groups will be assessed and separately analysed within a clinical prospective observational study: (1) 25 patients with sepsis or septic shock (according to sepsis-3 criteria), (2) 25 patients undergoing pancreatic surgery and (3) 25 healthy controls. Patients with sepsis and patients undergoing pancreatic surgery will receive standard therapy according to local protocols derived from international guidelines. In addition, cardiac output of perioperative patients and patients with sepsis will be measured. Healthy controls undergo one standardised evaluation. The TIVITA Tissue System is a novel HSI system that uses the visible and near-infrared spectral light region to determine tissue microcirculatory parameters. HSI analysis (hand/knee) will be done in parallel to haemodynamic monitoring within defined intervals during a 72-hour observation period. HSI data will be correlated with the Sequential Organ Failure Assessment score, global haemodynamics, inflammation and glycocalyx markers, surgical complications and 30-day outcome.

Ethics and dissemination The protocol has been approved by the local ethics committee of the University of Heidelberg (S-148/2019). Study results will be submitted to peer-reviewed journals and medical conferences.

Trial registration number DRKS00017313; Pre-results.

Strengths and limitations of this study

- ► First analyses of the combined hyperspectral imaging (HSI) parameters (haemoglobin oxygenation, near-infrared perfusion index, tissue haemoglobin index and tissue water index) using the TIVITA Tissue System in perioperative and critical care patients.
- ► Prospective observational study with hyperspectral measurements within a 72-hour timeframe.
- ► Single-centre observational study with 25 participants per group.
- ► Unknown transferability of HSI skin microcirculation data to microcirculation in other organs.
- ► Recruitment of patients with sepsis on a surgical intensive care unit could lead to selection bias.

INTRODUCTION

Microcirculatory alterations are associated with increased mortality and morbidity in critical illness.[1 2] Sepsis as well as the stress response to surgery are associated with a decoupling of macrocirculation and microcirculation termed haemodynamic incoherence.[1] Aiming to achieve macrocirculatory target parameters without monitoring of tissue perfusion and oedema increases the risks for adverse effects of fluids and vasopressors during resuscitation therapy. Therefore, clinical applicable bedside monitoring methods are required to improve microcirculatory diagnostics and reduce the adverse effects of haemodynamic incoherence. Non-invasive hyperspectral imaging (HSI) technologies for changes in skin microcirculation could broaden the spectrum of microcirculatory monitoring methods, but data on their use in critical illness are limited.

The skin is an easily accessible organ to examine microcirculatory alterations. Skin mottling and capillary refill time (CRT) are predictive of shock severity in critical illness.[3–5] A semi-quantitative scoring system for skin mottling reflects severity of organ failure and identifies patients with worse outcome.[5] CRT-targeted haemodynamic therapy has demonstrated promising results associated with less fluid administration and organ dysfunctions.[6] However, the inter-observer variability for CRT demonstrated contradictory findings and a variety of proposed cut-off values must be considered as limiting factors.[4 7]

Optical technologies like sublingual video microscopy (SVM) and near-infrared spectroscopy (NIRS) advanced our knowledge about microcirculatory alterations in critical illness.[3 4] SVM allows quantitative determination of microcirculatory alterations and has been associated with organ dysfunction and mortality.[3 4] Despite ongoing improvements, technical difficulties, time-consuming examinations and training requirements still limit clinical SVM use.[3 4]

NIRS offers a non-invasive bedside monitoring of tissue oxygenation and indirect blood flow evaluation.[3 4] NIRS can identify patients at risk for microcirculatory failure but vascular occlusion tests are required to provide a dynamic assessment of microvascular reserve. Technical limitations of NIRS include effects of tissue oedema at the sensor application site.[3 4]

HSI uses the visible and near infrared spectral light region to determine skin microcirculatory parameters.[8 9] Within one measurement of an arbitrary skin area, the novel HSI device TIVITA Tissue System offers a combined evaluation of haemoglobin oxygenation (StO_2), near-infrared perfusion index (NPI), tissue haemoglobin index (THI) and tissue water index (TWI).[8 10] This HSI system has been developed for integrative wound analysis.[8 10] The analysing software of the TIVITA Tissue System allows qualitative and quantitative bedside data interpretation.

The aim of the current study is to evaluate the feasibility of the TIVITA Tissue System for bedside microcirculatory monitoring in critically ill patients with sepsis and perioperative patients after pancreatic surgery. Therefore, we will investigate the association of the observed HSI parameters with organ dysfunction and common parameters of microcirculation and macrocirculation.

METHODS AND ANALYSIS

Trial design

This study is a prospective, observational clinical pilot study.

Harms

The study is observational, so that adverse events are not expected. All patients receive standard therapy and monitoring according to local protocols derived from international guidelines. The HSI measurements are non-invasive and contactless. Blood samples will be taken at the same time as other clinically necessary blood samples. Due to the small sample volume, there is only a minimal risk of harm as a result of participation. The occurrence of adverse events will be documented. Serious adverse events will be immediately reported to the project leader.

Recruitment

Patients diagnosed with sepsis will be recruited on admission to the surgical intensive care unit (ICU). Informed consent will be obtained from the patient or depending on the patient's clinical status a legal representative will be asked for participation. Final consent will be obtained in all patients with sepsis when/if they have recovered and regained full consciousness.

Patients undergoing elective pancreatic surgery will be informed and asked for participation on admission to hospital. Informed consent will be obtained from all volunteers of the healthy control group during an interview. All participants will be advised on the option of withdrawal from the study at any point in the process. Withdrawal from the study will be followed by the immediate deletion of the corresponding data set before the data has been anonymised or published. Study recruitment has started in June 2019 and is planned to be completed within the following 2 years.

Settings and participants

This single-centre study will be performed by the Department of Anaesthesiology of the Heidelberg University Hospital, Germany. In total, 25 patients with sepsis/septic shock, 25 patients undergoing pancreatic surgery and 25 healthy volunteers will be included.

Eligibility criteria

For eligibility to participate, patients must be older than 18 years and informed consent must be signed by the participant or a legal representative. A summary of all inclusion and exclusion criteria for the three groups is provided in table 1.

Sample size

Due to the explorative character of this observational study, no a priori sample size calculation was performed.

Patient involvement

For this study, no specific patient involvement actions are planned.

Outcomes

This observational study combines three independent groups under one protocol. This concept was selected as it provides similar observational timelines within the perioperative and critical care context.

Each group will be analysed separately because the clinical context and haemodynamic monitoring devices in the three groups are not interchangeable.

Table 1 Summary of inclusion and exclusion criteria of different study groups

All groups	
Global inclusion criteria	► Age ≥18 years ► Signed informed consent
Global exclusion criteria	► Refusal of participation ► Pregnancy
Sepsis group (sepsis and septic shock)	
Group-specific inclusion criteria	► Sepsis according to Sepsis-3 criteria[11]: ► A life-threatening organ dysfunction caused by a suspected or proven infection ► Acute change in total SOFA score ≥2 points ► Onset <24 hours ► Septic shock: patients with persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and serum lactate level >2 mmol/L despite adequate volume resuscitation
Pancreatic surgery group	
Group-specific inclusion criteria	► Elective pancreatic resection surgery with open approach ► Planned ICU admission after surgery
Group-specific exclusion criteria	► Atrial fibrillation (due to uncalibrated pulse contour analysis system)
Control group	
Inclusion criteria	► Healthy volunteers

ICU, intensive care unit; MAP, mean arterial pressure; SOFA, Sequential Organ Failure Assessment.

Primary outcome—sepsis and pancreatic surgery group

The primary outcome parameter is the correlation of HSI parameters with organ dysfunction severity assessed by SOFA score at the respective observation time points during the 72 hours observation period (either from sepsis onset (for patients with sepsis) or from surgery (for patients undergoing pancreatic surgery)).

Secondary outcome—sepsis and pancreatic surgery group

These include the correlation of HSI parameters with haemodynamic variables (eg, vasopressor support, fluid balance, heart rate, heart rate variability (HRV), blood pressure, cardiac index (CI)), lactate, glycocalyx marker and acetylcholinesterase (AChE)/butyrylcholinesterase (BChE) levels at the respective observation time points. The predictive value of HSI parameters for ICU and hospital length of stay, surgical complications and 30-day mortality will be investigated.

Control group

No data are currently available on the reference range of HSI values for TIVITA Tissue parameters in the investigated body areas (fingertips, palms, knees) and their association with macrohaemodynamic parameters in unstressed haemodynamic context. The healthy control group will be evaluated to examine the association of the TIVITA Tissue System HSI parameters for the first time with clinically relevant macrohaemodynamic parameters.

Participant timeline and involvement

Pancreatic surgery group

For patients undergoing pancreatic surgery, perioperative data, surgical procedure, blood loss, intraoperatively administered fluids, catecholamines, ventilator settings and anaesthetics will be collected from the clinical documentation. HSI measurements will be taken before induction of anaesthesia, after induction of anaesthesia, before anaesthesia emergence, 6 hours postemergence of anaesthesia and three times daily (08:00, 14:00, 20:00±1 hour) for a total observation period of 72 hours (9–12 measurements in total; table 2). Haemodynamic parameters (eg, CI, heart rate, blood pressure) will be documented simultaneously. The ProAQT system (PULSION Medical Systems SE) will be used for pulse pressure variation (PPV) and CI monitoring by radial artery pulse contour analysis (including CI, stroke volume variation (SVV), PPV).

At all timepoints of HSI assessment, blood gas analysis will be performed, including serum lactate measurement. Syndecan-1 and heparan sulfate are measured daily. AChE/BChE activity and HRV are measured contemporaneously to HSI. Standard perioperative and postoperative laboratory results including white blood cell count (WBC), C reactive protein (CRP) and procalcitonin (PCT), as well as medications, fluid balance, blood products and clinical scores will be acquired from the clinical documentation system.

Table 2 Timeline of perioperative patients over a total observation time of 72 hours

	Before induction of anaesthesia	After induction of anaesthesia	Before anaesthesia emergence	6 hours after end of surgery	08:00/14:00/20:00 hours for 72 hours	Day 30 after surgery
HSI	●	●	●	●	●	–
Macrohaemodynamic evaluation (HR, blood pressure, ProAQT)	●	●	●	●	●	
Serum lactate, blood gas analysis	●	●	●	●	●	
Glycocalyx parameters (syndecan-1, heparan sulfate)	●	●	●	●	One measurement/day	
AChE, BChE	●	●	●	●	●	
HRV	●	●	●	●	●	
Data from clinical documentation	●	●	●	●	●	●
Laboratory findings	●	●	●	●	●	
Surgical complications/ mortality						●

AChE, acetylcholinesterase; BChE, butyrylcholinesterase; HR, heart rate; HRV, heart rate variability; HSI, hyperspectral imaging.

Sepsis group

In patients with sepsis, clinical data, onset and suspected septic focus will be documented. HSI parameters of patients with sepsis will be measured on admission to the ICU, 6 hours afterwards and three times a day (08:00, 14:00, 20:00 hours±1 hour) for a total observation period of 72 hours (9–12 measurements in total; table 3). Basic haemodynamic monitoring variables (including heart rate, pulse oximetry, blood pressure, urine output), ventilator settings, vasopressors, transfusion requirements and fluid balance will be documented. In patients with sepsis, the PICCO system (PULSION Medical Systems SE) will be used for combined pulse contour analysis and transpulmonary thermodilution (including CI, SVV/PPV, extravascular lung water index) monitoring.

At all timepoints of HSI assessment, blood gas analysis will be performed, including serum lactate measurement. Syndecan-1 and heparan sulfate in serum will be measured daily. AChE/BChE activity and HRV will be measured contemporaneously to HSI parameters. Standard laboratory results, inflammatory biomarkers WBC,

Table 3 Timeline of patients with sepsis over a total observation time of 72 hours

	Admission to ICU	6 hours after admission	08:00/14:00/20:00 hours for 48 hours	Day 30 after admission
HSI	●	●	●	
Macrohaemodynamic evaluation (HR, blood pressure PICCO measurements)	●	●	●	
Serum lactate, blood gas analysis	●	●	●	
Glycocalyx parameters (syndecan-1, heparan sulfate)	●	●	One measurement/day	
AChE, BChE	●	●	●	
HRV	●	●	●	
Data from clinical documentation	●	●	●	●
Laboratory findings	●	●	●	
Surgical complications/mortality				●

AChE, acetylcholinesterase; BChE, Butyrylcholinesterase; HR, heart rate; HRV, heart rate variability; HSI, hyperspectral imaging; ICU, intensive care unit.

CRP and procalcitonin PCT, as well as clinical scores will be acquired from the clinical documentation system.

Patients in the sepsis and the pancreatic surgery groups will receive therapy according to national and international guidelines adapted to local protocols at the discretion of the care-giving physician.[11 12] All study measurements will be performed by an investigator not involved in direct patient care. HSI results will not be available to the treating physician.

Control group

In addition to HSI measurements, weight, height, sex, oxygen saturation, heart rate, blood pressure, HRV will be measured. Echocardiography will be performed according to international recommendations.[13 14] Cardiac output will be evaluated by using the left ventricular outflow tract (LVOT) diameter and the velocity time integral in the LVOT. Echocardiography will be performed by one certified examiner (European Diploma in advanced intensive care EchoCardiography certified).

End point description

Hyperspectral imaging

The TIVITA Tissue System (Diaspective Vision GmbH, Am Salzhaff, Germany) was developed for wound diagnostics.[10 15] The camera captures the visible and invisible fraction of the light spectrum (500–1000 nm) and offers a non-invasive spectroscopic chemical analysis of the examined tissue compound including StO_2, NPI, THI and TWI.[8 10] Within 30 s, the recorded HSI data are integrated into a two-dimensional picture with high spatial and spectral resolution.

StO_2 and NPI measure the haemoglobin oxygen saturation with a penetration depth up to 1 mm and 4–6 mm, respectively. THI shows the haemoglobin distribution in the microcirculatory system while TWI measures the water content of the tissue. The analysing software allows bedside quantitative and qualitative data evaluation.

Parallel assessment of three perfusion parameters (StO_2, THI and NPI) in different tissue depths could allow a comprehensive spatial evaluation of skin perfusion. A unique feature of this camera system is a parallel evaluation of tissue water by TWI and tissue perfusion.

Manufacturer guidelines will be followed during HSI measurements to reduce external light disturbances to avoid effects on parameter calculation. There are no clinical data on the impact of melanin on the TIVITA measurements in patients with different skin colours. Possible effects of skin melanin will be separately analysed.

Glycocalyx marker

The endothelial glycocalyx of the vascular wall is an intraluminal layer of glycoproteins, proteoglycans and glycosaminoglycans. Glycocalyx degradation results in vascular hyperpermeability and tissue oedema. In the blood of patients with sepsis and patients following major surgical interventions, elevated glycocalyx markers (eg, syndecan-1, heparan sulfate) can be detected and correlate with microvascular wall damage.[16 17] A relationship between HSI assessed TWI and glycocalyx degradation has not yet been investigated.

Butyrylcholinesterase and heart rate variability

Compared with healthy volunteers, patients with sepsis show a reduced BChE activity, which correlates inversely with the disease severity.[18] Physiologically, the heart rate is subject to spontaneous fluctuations even at rest. These can be measured as HRV by a special ECG. In patients with sepsis and trauma patients, the HRV is reduced and shows an inverse correlation with the disease severity and mortality.[19] Cholinergic system parameters AChE and BChE are measured contemporaneously to hyperspectral parameters (Point-of-Care Lisa System, Dr Franz Köhler Chemie GmbH) and HRV (DMS 300-4 L ECG Recorder, MTM GmbH).

Follow-up

The 30-day survival and surgical/medical complications within 30 days from study inclusion will be collected from the clinical documentation or will be inquired by telephone request from patients in the sepsis and the pancreatic surgery groups. For the healthy control group one single examination without follow-up is planned.

Statistical analysis

Data will be collected with the aid of an electronic database system (Microsoft Excel (Microsoft Deutschland GmbH, Unterschleißheim)). GraphPad Prism (GraphPad Software, La Jolla, California, USA, www.graphpad.com) will be used for statistical analyses. Statistical analyses will be performed within each group between different points in time within the 48-hour and 72-hour observation period. Descriptive statistics will be applied for the complete dataset. For continuous variables and scores, mean, SD, minimum, median and maximum will be calculated. The absolute and relative incidence of categorical variables will be presented. Spearman's rank correlation will be applied to values of HSI parameters with haemodynamic parameters and SOFA score in the patient groups and correlation of HSI values with macrohaemodynamic variables in the control group. Change over time will be assessed using Friedman tests for each group, respectively. To evaluate a possible predictive value of HSI parameters, logistic regression analyses will be applied for binary outcome measures (eg, outcome) and linear regression models for continuous measures. Results of statistical tests must be considered as descriptive.

Data deposition

Participants' data will be pseudonymised and stored in an electronic database on an internal password-secured server. After complete analysis and publication, the study data will be anonymised and stored in the archive of the department for 10 years.

ETHICS AND DISSEMINATION

Verbal and written information regarding informed consent will be presented to the caregivers. Before the beginning of the clinical trial, the study protocol, the patient information

and informed consent and all other required documents will be submitted to the Ethics Committee of the Medical Faculty of Heidelberg. Positive ethical vote has been given by the Ethics Committee of the Medical Faculty of Heidelberg, Trial Code No. S-148/2019. Changes to the protocol are made in writing and require the approval of all signatories of the protocol. Subsequent amendments also require a positive assessment from the competent ethics committee. Described procedures are meant to ensure that all parties involved abide by the principles of Good Clinical Practice and those stipulated in the Declaration of Helsinki.[20 21] The conducting takes place in accordance with local statutory and implementing provisions. The findings of this study will be submitted to peer-reviewed journals for publication following the Strengthening the Reporting of Observational Studies in Epidemiology guideline.[22] The data will be presented at relevant national and international conferences.

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