Renal perfusion and the development of AKI following traumatic injury – A longitudinal observational cohort study.

Short Title: The PERTAKI study

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Contents

1. Background and rationale

Critically ill trauma patients are at an increased risk of developing acute kidney injury (AKI), the incidence of which is between 20 and 24% [Perkins: 2019]. In addition, the presence of AKI in this patient population is associated with a marked increase in mortality risk [Søvik: 2019]. Traditionally systemic haemodynamic status, especially intra-vascular volume, has been viewed as a critical factor in the development of AKI. However, such an understanding considerably over simplifies the situation and it is increasingly clear that the development of AKI depends on a number of interlinking factors including age, pre-traumatic comorbidity, sepsis, the nature of the traumatic insult, administered therapies and a complex interplay between macro and micro-circulatory blood flow [Søvik: 2019].

Modern trauma management includes early blood product resuscitation, permissive hypotension and early damage control surgery. However, the generally accepted resuscitative target of a mean arterial pressure (MAP) of 65 mmHg lacks precision as a marker of adequate tissue perfusion. Following this non-precise goal directed resuscitative strategy therefore risks the excessive administration of blood or fluid. This is of concern due to the growing body of evidence which suggests that a positive fluid balance may be associated with harm in the critically ill. Specific to critically ill trauma patients, higher fluid administration after the initial resuscitative window has been shown to be associated with increased morbidity [Mezidi: 2017].

Renal contrast enhanced ultrasound (CEUS) offers an opportunity to assess small vessel related renal perfusion in an objective fashion and has been tested for efficacy and safety in several small clinical series [Wang: 2016, Schneider: 2013 & Schneider: 2014]. In a recent study conducted by our group CEUS demonstrated renal cortical microcirculatory dysfunction to be associated with the development of AKI in patients with septic shock [Watchorn: 2022]. This finding was independent of macrovascular flow and not associated with other markers of microcirculatory impairment. In the shocked trauma patient it is not known whether the same association exists. This is important because greater understanding of tissue perfusion and its association with AKI in this patient population may open opportunities to individualised resuscitation protocols aimed at prevention of this important sequelae of trauma and risk factor for mortality.

2. Aims

The primary aim of the study is to investigate the degree to which acute kidney injury following circulatory shock as a result of traumatic haemorrhage is a consequence of macro and /or micro circulatory dysfunction. Secondary aims are to investigate the relationship between the systemic and renal microcirculation and macrocirculation over time in patients with haemorrhagic shock. Completion of the study will provide data to enable construction of an interventional study designed to reduce the incidence of kidney injury in patients with significant trauma.

3 Study design

3.1 Overview

Prospective longitudinal observational study. Serial and continuous measurements will be made using non-invasive monitoring modalities in order to assess systemic and renal blood flow and tissue perfusion. Blood and urine samples will be taken contemporaneously to facilitate later mechanistic analyses.

3.2 Setting

Single tertiary intensive care unit.

3.3 Population

Adult patients with traumatic haemorrhagic shock.

3.3.1 Inclusion Criteria

Age > 18 years
Within 24 hours of ICU admission following traumatic injury
Received any blood products during initial resuscitation
Lactate > 2 mmol/l at any stage prior to study enrolment

3.3.2 Exclusion criteria

Known intolerance to Sonovue™ or any other ultrasound contrast agent
Patients with un-survivable injuries / not expected to survive 24 hours in whom the intent of treatment is palliative
Known CKD 4 or end stage renal failure

Pregnancy

3.3.3 Co-enrolment

Co-enrolment is permitted for both observational and interventional studies.

3.3.4 Screening

Daily screening will take place and details of eligible patients will be entered into a screening log. Eligible patients will be identified by attending clinical staff and notified to the research team. Reasons for non-recruitment of eligible patients will be recorded in the screening log.

3.4 Recruitment and consent

3.4.1 Overview & rationale

Patients with traumatic haemorrhagic shock, eligible for inclusion in the study, are critically unwell, potentially receiving sedative medications and frequently exhibiting both a reduced level of consciousness and inability to effectively communicate. For all these reasons, they typically lack capacity to provide prior informed consent. The point of maximal scientific interest and potential for future treatment developments occurs in the first hours of critical illness during this period of mental incapacity. For these reasons any attempt to obtain either prior informed consent from the patient, or the opinion of their Personal Consultee (i.e. relative or close friend), prior to study enrolment would be inappropriate.

In view of these considerations, once an eligible patient is identified for the trial (i.e. the patient meets the inclusion criteria and does not meet any exclusion criteria), they will be enrolled into the study. This method is known as 'deferred consent' or 'research without prior consent' and is recognised in law. This process will be covered by an emergency waiver of consent under the Mental Capacity Act approved by (INSERT REC REF)

3.4.2 Informed deferred consent

Following enrolment, patients will be approached once they have been deemed to have full capacity to provide informed deferred consent. A Participant Information Sheet (PIS) will be provided to the patient. The PIS will provide information about the purpose of the study, what participation means for the patient, confidentiality and data security, and the future availability of the trial results.
A Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without

consequence; and that consent is given for access to medical records for data collection. The Consent Form will also cover ongoing data collection and follow-up.

Patients will be given time to read the PIS and have an opportunity to ask any questions they may have about participation in the study. After verifying that the PIS and Consent Form are understood, the person seeking consent will invite the patient to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the patient, a copy placed in the patient's medical notes and the original kept in the Site File. If the patient is unable to physically sign the Consent Form (e.g. due to physical incapacity), an independent witness can sign on their behalf.

3.4.3 Role of personal consultee

As out lined in Section 3.4.1-2 it will usually not be possible to involve trial participants in the consenting process early on. Instead, consent will be obtained from patients once they have stabilised and are deemed to have capacity.

In the interim, once notified of the enrolment of a patient into the study, a delegated member of the research team will approach the Personal Consultee as soon as appropriate and practically possible to discuss the trial and to seek their opinion as to the patients' likely wishes and feelings regarding participating in research. Ideally, this approach would take place within 24-48 hours of randomisation, once the patient's medical situation is no longer an emergency and initial meetings between the consultee and treating clinicians have occurred.

The Personal Consultee will be provided with a Personal Consultee Information Sheet, containing all of the information provided on the PIS, supplemented by information about why the Personal Consultee has been approached at this stage. A Personal Consultee Opinion Form will be provided indicating that: the information given, orally and in writing, has been read and understood; the patients' participation is voluntary and can be withdrawn at any time without consequence; and that, in the Personal Consultees opinion, the patient would not object to taking part in research. Personal Consultees will also be asked to indicate on the Personal Consultee Opinion Form whether, in their opinion, the patient would agree to access to medical records for data collection.

Personal Consultees will be given time to read the Personal Consultee Information Sheet and have an opportunity to ask any questions they may have about the patients' participation in the study. After verifying that the Personal Consultee Information Sheet and Opinion Form are understood, the

person seeking opinion will invite the Personal Consultee to sign the Personal Consultee Opinion Form and will then add their own name and countersign it. A copy will be given to the Personal Consultee, a copy placed in the patient's medical notes and the original kept in the Site File. If a Personal Consultee advises that, in their opinion, the patient would not choose to participate in research, then no further data collection will occur.

Upon patient recovery, the patient will be approached directly for informed deferred consent (see section 3.4.2). The patient's decision will be final, and will supersede the Personal Consultee, where there is disagreement.

3.4.4 Event of patient death

In the situation where the patient has died, a Nominated Consultee will be appointed. The Nominated Consultee will be an independent clinician (i.e. not associated with the conduct of the trial). Opinion of the Nominated Consultee will be sought in the same manner as for the Personal Consultee.

A Nominated Consultee will also be approached in the rare situations where no Personal Consultee is available (or one is available but unwilling to provide opinion). Upon patient recovery, the patient will be approached directly for informed deferred consent (see section 3.4.2). The patient's decision will be final, and will supersede the Nominated Consultee, where there is disagreement.

3.4.5 Event of discharge / transfer prior to recovery of capacity

In the rare situation where the patient is transferred to another hospital prior to consent being sought, then the most appropriate member of the site research team will liaise with the receiving hospital on a weekly basis to establish at which point capacity has been regained and when discharge is probable. Following hospital discharge the patient will be sent a covering letter, personalised by the most appropriate clinical team member, and a copy of the PIS and Consent Form by post. The letter will direct the patient to the PIS for detailed information on the trial and provide telephone contact details if the patient wishes to discuss the trial with a member of the research team. The letter will ask the patient to return the Consent Form to confirm whether they would be content for collected data to be used.

If there is no response after four weeks of sending the covering letter, a follow-up letter, alongside second copies of the PIS and Consent Form, will be sent to the patient. This second letter will

provide the same information as the first letter, but will confirm that if no Consent Form is received within four weeks of the letter being sent, then the participant's data will be included in the trial unless they notify the site research team otherwise.

3.5 Data collection

Data collection using the subject devices (cardiac echocardiography, renal contrast enhanced ultrasound and sublingual video microscopy) will be undertaken at study enrolment (D0), and at 24 and 48 h later (D1, D2). Urinary partial pressure of oxygen (pO2) will be measured continuously from D0 to study completion. All procedures will be undertaken by a study investigator specifically trained in the individual techniques.

3.5.1 Trans thoracic echocardiography including use of contrast

Transthoracic echocardiography will be performed using an Affiniti Ultrasound System (Philips, UK) and standard windows obtained (parasternal long axis, parasternal short axis, Apical 4 chamber, Apical 5 chamber, Apical 2 chamber, subcostal 4 chamber).

Following acquisition of standard images 2.4 ml of ultrasound contrast medium (Sonovue™, Bracco SpA, Milan, Italy) will be injected via the intra venous route. Further contrast enhanced images will be obtained for off line analysis. Images will be identified by study number rather than identifiable details.

3.5.2 Incident dark field video-microscopy

Videos of the sublingual microcirculation will be acquired using an Incident Dark Field (IDF) video-microscope (Cytocam, Braedius Medical, Huizen, The Netherlands).

Following suctioning of the oropharynx, a gauze swab will be applied to gently remove saliva from the mucosal surface. The camera probe will be applied to the sublingual area and images selected, taking care to exclude areas of buccal microcirculation with large numbers of looped vessels. The device will be focussed until individual erythrocytes can be visualized within capillaries and the brightness setting adjusted to produce an acceptable degree of contrast between blood vessels and background tissue. At all times pressure artefact will be scrupulously avoided by applying only the minimal amount of pressure necessary to obtain an image. Stopped or reversed flow in larger venules will be taken as a sign of pressure artefact, necessitating adjustment of the camera or selection of a different area of the microcirculation for observation. A minimum of 3, and ideally 5,

video images of the sublingual microcirculation will be taken at each experimental time point, each recorded clip consisting of 100 video frames at a rate of 20 frames per second.

Images will be analysed offline using Automated Vascular Analysis (AVA) software. Images will be identified with the study number and no patient identifiable details will be included.

3.5.3 Renal ultrasound including use of contrast

Renal ultrasound, including the use of contrast, will be performed using an Affiniti ultrasound system (Philips, UK).

Conventional grayscale US imaging will be performed. The investigator will vary the pulse repetition frequency, focal zone, gain, and wall filter as necessary to obtain optimal sonograms in each case. Both kidneys will be visualized and the most accessible chosen to perform the study. Baseline grayscale and colour Doppler sonographic images will be recorded.

A low–mechanical index (MI) technique (range: 0.04 – 0.1) for CEUS will be utilised with MI set at or below 0.10. A bolus injection of 2.4 mL of SonoVue™ (Bracco SpA, Milan, Italy), contrast agent, will be administered followed by a 10mL flush with 0.9% saline.

Images of the entire examination will be digitally recorded. The recording of the examination is initiated at the start of the contrast injection and all time measurements started from these moments, which are defined as “time-0” in all recorded video clips. Measurements will be concluded after approximately 2 minutes.

Post-processing will then be performed offline with dedicated software to permit objective quantitative analysis.

3.5.4 Continuous urinary partial pressure of oxygen

Continuous urinary pO2 will be measured using the Oxylite™ single channel dissolved oxygen and temperature monitor (Oxford Optronix, UK) alongside pO2 probe consumables. The pO2 probe is inserted through a standard foley catheter. In the rare event that a patient does not already have a catheter in situ one will be inserted using the Sponsor’s approved urinary catheterisation technique. Measurements will be identified with the study number and no patient identifiable details will be included.

3.6 Outcome measures

Patients will be characterized by the worst degree of AKI in the 28 day period following ICU admission. Definitions of AKI will follow the KDIGO guidelines.

Systemic and renal perfusion variables over time and continuous urinary pO2 will be compared for groups of patients with KDIGO grades 1,2,3.

3.7 Data collection

This trial will be coordinated from the Anaesthetics, Critical Care, Emergency Medicine and Trauma (ACET) research team at KCH. Data will be collected by local investigators. Only data as set out on the Clinical Report Form (CRF) will be collected for this study.

3.8 Data management

All participant data collected will be entered onto a paper CRF before being transferred to an electronic spreadsheet. The PI will oversee and be responsible for data collection, quality and recording.

Security of the electronic spreadsheet is through restricted access permissions. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act.

4 Safety Monitoring & Reporting

4.1 Safety Issues relating to Sonovue contrast medium

There is only one specific identified safety issue associated with this observational study and that relates to the use of the intravenous contrast agent.

This agent consists of a solution of stabilised microbubbles filled with sulphur hexaflouride. The safety profile of this agent is good and has been extensively reported. In a series of 23,188 administrations reported in an Italian series there were a total of 29 (0.12%) reported adverse events but only 2 (0.009%) of these were classified as serious. Of the 2 serious adverse events one manifested as bronchospasm and mild hypotension which recovered within 30 minutes without requiring ventilatory support. The second incident was associated with severe hypotension, rash and drowsiness. Again, this resolved within 30 minutes.

The non-severe AEs reported in this series include dizziness, paraesthesia, itching and rash.

2 smaller case series have reported on the use of Sonovue to assess renal perfusion in critically unwell patients. The first investigated the effect of noradrenaline on renal perfusion (n=12), the second the effect of cardiac surgery on renal perfusion (n=12). No adverse events were reported in these two series.

Post marketing surveillance provided by the manufacturer of Sonovue™ reveals use in 2,447,083 patients between 2001 and 2012. 322 (0.0162%) serious adverse reactions were reported although causality was not clearly established in every case. There have been no fatal reactions reported.

4.2 Definitions

Adverse Event

An Adverse Event (AE) is any untoward medical occurrence affecting a trial participant during the course of a clinical trial. All eligible study patients are by definition critically unwell with the propensity to develop multiple adverse events. In addition, involvement in the study protocol, by virtue of its observational nature, is highly unlikely to be the cause of many observed adverse events. The exception to this is the potential for allergic reactions to the injected microbubble contrast medium as discussed below.

Serious Adverse Event

A Serious Adverse Event (SAE) is an adverse event that:

· Results in death
· Is a life-threatening situation
· Requires prolongation of hospitalisation
· Results in persistent or significant disability or incapacity

Relatedness

None: there is no evidence of any relationship to the study treatment

Unlikely: there is little evidence to suggest a relationship to the study treatment, and there is another reasonable explanation of the event

Possibly: there is some evidence to suggest a relationship to the study treatment, although the influence of other factors may have contributed to the event

Probably: there is probable evidence to suggest a relationship to the study treatment, and the influence of other factors is unlikely

Definitely: there is clear evidence to suggest a relationship to the study treatment, and other possible contributing factors can be ruled out.

Expectedness

Expected: The follow events are defined as expected AEs. These events are all possible manifestations of contrast related allergic reactions:

- Bronchospasm
- Hypotension (fall of > 10 mmHg from pre-administration baseline)
- Rash
- Itching
- Dizziness

Unexpected: Other events not listed above.

4.3 Recording and reporting AEs

AEs and SAEs must be reported in the participant's medical notes, on the study report form, and reported to the PI within 24 hours. The PI will assess the event for relatedness and expectedness. In the event that the PI decides that the event was related to contrast administration, or is unable to positively exclude such an association, the patient will be withdrawn from the study and no further measurements taken. Any SAEs associated with the administration of contrast medium will be reported to the REC in an expedited fashion within 15 days.

5. Study closure

5.1 Data archiving

Data will be archived for 3 years after study closure.

6. Statistics and data analysis

All images will be assessed offline by a single operator.

6.1 Analysis of microcirculation images

Video microscopy images will be assessed using AVA software to produce the following data:

Total Vessel density (TVD)
Perfused Vessel Density (PVD)
Microvascular Flow Index (MFI)
Microvascular Heterogeneity Index (MHI)

6.2 Analysis of contrast ultrasound images

Regions-of-interest (ROIs) will be manually drawn: 1 on an interlobar artery, 1 in the renal cortex, 1 in the renal medulla, and a ROI containing the entire kidney. The ROIs for the cortex and medulla will be identical in size for every clip and drawn at approximately the same depth. For every ROI, the software determined mean pixel intensities, proportional to contrast-agent concentration, will be used to create a time-intensity curve (TIC).

Based on the time-intensity curve, peak enhancement (PE), wash-in area under the curve (WiAUC), rise time (RT), mean transit time (mTT), time to peak (TTP), wash-in rate (WiR), wash-in perfusion index (WiPI; WiAUC/RT), wash-out area under the curve (WoAUC), total area under the curve (AUC), fall time (FT), and wash-out rate (WoR) will be analysed. Parameters related to blood volume are PE, WiAUC, WoAUC and AUC. The other parameters, i.e. RT, mTT, TTP, WiR, WiPI, FT, WoR, are related to blood velocity. Renal perfusion could also be assessed based on the Perfusion Index through CEUS replenish kinetics.

7. Ethical compliance and standards

Patients eligible for enrolment in this study will lack capacity to provide informed consent. The ethical procedures this study will follow are based on the guidance provided in the Mental Capacity Act 2005 and adhere to the principals laid down within the Declaration of Helsinki. We will seek regulatory approval to waive consent to facilitate early recruitment. However, at the earliest possible opportunity we will seek to obtain approval from the patient's surrogate decision maker (e.g. close friend or relative) to allow continuing participation in the study. Once the patient regains capacity they will be approached to consent for use of data. We have used this approach in three previous research studies involving critically ill patients, which all received ethical approval.

The PERTAKI study will be conducted in accordance with the approved trial protocol, ICH-GCP guidelines, the Data Protection Act (1998) and the Mental Capacity Act (2005).

7.1 Study registration

The study will be registered with an appropriate clinical trial registry prior to commencement.

7.2 Central ethical compliance

The study will be reviewed by a REC through the normal IRAS process.

The PI will submit annual progress reports and all protocol amendments to the REC for review.

8. Data handling and management

The study complies with the principles of the Data Protection Act, 2018. At all times researchers will act to preserve the confidentiality of patient identifiable data.

Patients will be de-identified by allocation of a unique study number and collected data will be referred to by this study number rather than to personal identifiable information. Personal data, including full name, date of birth and NHS number will be required to successfully follow-up enrolled patients and will be linked to collected data on a separate electronic spreadsheet. Only members of the immediate research team will have access to personal identifiable data. Personal data will not be retained after follow up is complete and will be deleted at this time. The research team will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified.

All physical data, such as CRF and Consent Forms will be securely stored in a locked research office.

All electronic data will be maintained on a secure electronic database accessible only by members of the research team.

De-identified data will be retained indefinitely within the sponsors institution.

9. Storage of Biological Samples

In the study, blood and urine will be collected from patients in accordance with the patient consent form and patient information sheet. Samples will be processed, stored and disposed in accordance with all applicable legal and regulatory requirements, including the Human Tissue Act 2004 and any amendments thereafter.

Samples will be de-identified by allocation of a unique study number.

Samples will be stored within the James Black Centre, part of King's College London.

De-identified samples may be shared with other academic institutions. Permission for this will be explicitly sought during the initial consent process.

10. Sponsorship and Funding

10.1 Sponsoring Organisation

The study is sponsored by King's College Hospital NHS Foundation Trust.

10.2 Funder

The study is funded by the Medical Directorate of the Defence Medical Services, part of the UK Ministry of Defence.

11. Dissemination of results

The results of the PERTAKI study will be widely and actively disseminated through publication in peer reviewed medical journals and presentations at national and international meetings.

12. Peer and regulatory review

The study has been peer reviewed in accordance with the requirements outlined by the Sponsor. The Sponsor considers the procedure for obtaining funding from the Research Directorate of the Defence Medical Services to be of sufficient rigour and independence to be considered an adequate peer review.

The study was considered and received a favourable opinion from the XX Research Ethics Committee (INSERT REC REF)

13. Indemnity Arrangements

King's College Hospital will provide NHS indemnity cover for negligent harm, as appropriate, and is not in the position to indemnify for non-negligent harm. NHS indemnity arrangements do not extend to non-negligent harm and NHS bodies cannot purchase commercial insurance for this purpose; it cannot give advance undertaking to pay compensation when there is no negligence attributable to their vicarious liability. The Trust will only extend NHS indemnity cover for negligent harm to its employees, both substantive and honorary, conducting research studies that have been approved by the R&D Department. The Trust cannot accept liability for any activity that has not been properly registered and Trust approved. Potential claims should be reported immediately to the R&I Office.