York Teaching Hospital
NHS Foundation Trust

AutoFlow

Data collection to develop ways to predict brain blood flow

Data Collection for the
Development of algorithms for prediction of the limits of autoregulation for cerebral and renal blood flow during major surgery with continuous invasive and non-invasive blood pressure measurements

IRAS ID: 290456

Protocol Version 2.0
9th November 2020

Authorised by:

Name:	Dr Simon Davies	Role:	Chief Investigator
Signature:		Date:	9/11/2020

General Information

This document describes the data collection study and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. Clinical problems relating to this study should be referred to the Chief Investigator.

Compliance

The study will be conducted in compliance with the protocol, GCP, GDPR, NHS research governance, the Declaration of Helsinki, and the terms of the favourable opinion from the National Research Ethics Service.

Sponsor

York Teaching Hospital NHS Foundation Trust will act as Sponsor for the study.
York Hospital
Wigginton Road
York
YO31 8HE

Funder

Funding will be from Edwards Lifesciences Ltd

Authorisation

Dr Simon Davies and Prof Thomas Scheeren are authorised to sign the final protocol and protocol amendments.

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1.Background

The brain has a high metabolic demand and receives about 12% of cardiac output (CO) (1). This high metabolic demand makes the brain at risk for injury when disturbances in hemodynamic status occur, e.g. during surgery. However, cerebral autoregulation is responsible for protecting the brain from injury caused by hemodynamic changes (2,3). The concept of cerebral autoregulation, including a lower limit, a plateau and an upper limit, was proposed in 1959 (4), which means that when cerebral perfusion pressure (CPP) is in the range between 50 and 150 mmHg cerebral blood flow (CBF), and hence oxygen delivery remains more or less constant by adjusting vascular resistance (3). A combination of myogenic, neurogenic, metabolic, and endothelial mechanisms are responsible for maintaining cerebral autoregulation (3). In case of an increase in CPP, local vasoconstriction occurs and in case of a decrease in CPP, vasodilatation occurs to maintain constant CBF. Cerebral perfusion pressure is calculated as mean arterial pressure (MAP) minus intracranial pressure and central venous pressure, and can be substituted by MAP when no elevation in intracranial pressure is suspected (5). When CPP or MAP reach values outside of the autoregulation range, CBF will become directly dependant on blood pressure resulting in decreased CBF and hence oxygen delivery which may result in postoperative neurologic complications.

Cerebral oxygenation as a surrogate of CBF in the assessment of cerebral autoregulation (5), can be measured by near-infrared spectroscopy (NIRS) and is increasingly used in the routine clinical care as cerebral oxygenation values have been associated with postoperative neurologic and general complications (6). The ForeSight Elite sensor technology allows for effective tissue interrogation by incorporating 5 wavelengths of near-infrared light to analyse tissue, providing a broad spectrum of NIRS wavelengths (685, 730, 770, 810, 870nm). This allows for effective tissue interrogation at points where oxygenated and deoxygenated haemoglobin are more greatly distinguished for highly accurate performance. The sensors are non-invasive and placed on the forehead and can measure tissue oxygenation to a depth of 2.5cm.

Using blood pressure measurements and by examining changes in cerebral oxygenation autoregulation curves can be created as well as upper and lower limits of autoregulation as has been previously performed (7–10). The trend in

hemodynamic monitoring however is to progressively use less invasive monitoring tools.

The Clearsight™ non-invasive hemodynamic monitoring technology measures blood pressure using the volume clamp method developed by the Czech physiologist Jan Penaz (11,12). Using a simple non-invasive finger cuff, the volume of an artery is kept clamped at a constant diameter. Changes in diameter are measured by a photo-plethysmograph within the finger cuff, and a servo controller applies counter pressure to keep the diameter of the artery constant. This allows the measurement of beat to beat blood pressure and with additional algorithms cardiac output can also be calculated. The simple and non-invasive nature of this device makes it suitable to use in patients undergoing repair of fractured neck of femur regardless of the type of anaesthetic. It requires no calibration, and would make goal directed therapy accessible to this group. The Clearsight has been shown to be a valid measure of cardiac output and blood pressure(13).

A recent meta-analysis showed that several studies found invasive blood pressure monitoring interchangeable with finger cuff technologies, however the pooled results showed the contrary and that both were not interchangeable in surgical or critically ill patients (14). Hence autoregulation limits mapped by invasive blood pressure monitoring may not reflect those mapped by this less invasive technology.

The kidneys also have an autoregulation system to protect themselves from disturbances in hemodynamic status (15). Similar to the brain, in case of an increase in renal perfusion pressure (RPP), vasoconstriction occurs and in case of a decrease in RPP, vasodilatation occurs to maintain constant renal blood flow (RBF). The two mechanisms responsible for renal autoregulation are the myogenic response and the macula densa tubuloglomerular feedback (MD-TGF) response (16). The concept of an upper and lower limit also applies to renal autoregulation.

2. Rationale and Aim

The aim of this study is to acquire data that will allow to create cerebral and renal autoregulation curves and assess the agreement between invasive and non-invasive blood pressure measurements in patients undergoing elective surgery requiring continuous invasive hemodynamic monitoring. Blood pressure measurements will be

obtained invasively with an arterial catheter and non-invasively with the ClearSight sensor applied to one of the fingers, whilst cerebral and renal oxygenation is measured by NIRS. The data collected will also be used to help develop predictive algorithms for cerebral desaturation.

2.1 Risks and benefits.

There are no additional benefits for individuals taking part in this study

As with all optical sensors (ForeSight), there is the theoretical risk of thermal burn. The design includes safeguards, and this risk is believed to be minimal. Sensors will be attached with adhesive and may be secured by a supplemental headband. Optical exposure is minimized by procedure and low power. Overall risk is estimated to be low for the ForeSight sensors and site check are performed on a regular basis. Additionally, the ClearSight sensors could theoretically pressure damage if placed to tightly, however this risk is also estimated as low, and no reported cases have been described.

3. Study Sites

This study will take place in the surgical unit, operating theatres and post anaesthetic care unit, York Hospital, Wigginton Road, York YO31 8HE, and the surgical unit, operating theatres and post anaesthetic care unit of the University Medical Centre Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands.

4. Selection of Patients

4.1 Patient inclusion criteria.

Patients due to undergo elective major non-cardiac surgery requiring invasive arterial monitoring (decided at the discretion of the treating clinician) under general anaesthesia, and with an expected duration of greater than 90 minutes,

4.2 Patient exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Subject has skin abnormalities affecting the forehead, flank or skin of the upper leg that would prevent monitoring of tissue oxygenation during the study
- Patients undergoing cardiac surgery with cardiopulmonary bypass (non-pulsatile blood flow)
- Age < 18 years

4.3 Number and source of patients and participants .

100 patients undergoing major non cardiac surgery will be recruited – 50 from each participating site.

4.4 Identification, recruitment and consent.

The identification and consent process is described below, and only patients with capacity will be recruited

Patients scheduled for major elective surgery that meet the inclusion criteria will be given the Patient Information Leaflet at the earliest opportunity. Patient Information Leaflets will be posted to potential participants with their pre-operative assessment information, or alternatively given out by one of the researchers or research nurses at the pre-operative assessment clinic. During normal working hours, a member of the research team will be available to answer any questions relating to the research project. All members of the research team will have an in-depth knowledge of the protocol and all have been involved in various research projects using this technology. Once the Patient Information Leaflet has been given out, a sticker will be placed in the clinical notes stating that the patient is eligible for the study and has been given the information. This sticker will be timed and dated. Those patients eligible to take part will be asked to consent having had time to consider the proposal. Consent will be received either by the Chief Investigator, the Co-Investigators or an appropriately trained Research Nurse, and will normally take place at either the pre-operative assessment clinic or on admission to hospital depending on when the individual received the patient information sheet. Another sticker will be placed in the notes stating that informed consent has been received. Again, this will be timed and dated. Three copies of the consent form will be taken –

the original for the site file, one copy for the patient and one to go into the patient's notes.

If people withdraw from the study, data collected until the point of withdrawal will be included in the study.

4.5 Screening procedures and pre-randomisation investigations.

Electronic theatre lists will be screened to find patient subjects eligible for the study. This is the only screening procedure. No other investigations are necessary for the conduct of this study. Patients will receive their standard pre-operative work-up, irrespective of whether they participate in the study or not. A decision to withdraw, or a decision not to take part will not affect the standard of care that the patient receives.

5. Allocation

5.1 Allocation to treatment

This will be a prospective non randomised observational study recruiting 50 sequential patients at both sites. There is no allocation to treatment and all subjects will receive standard institutional care.

5.2 Co-enrolment guidelines.

For the duration of their involvement in this study, patients may be co-enrolled in other perioperative studies as long there is no intervention performed during the intraoperative period. This would include observational studies and interventional studies where the intervention is performed after recovery from anaesthesia.

6. Treatment of Patient Participants

When the participant arrives in the operating room they will be connected to standard monitoring including non-invasive blood pressure, ECG and SpO_2. An arterial cannula (standard care) will be placed in a radial artery (brachial artery if radial is

unable to be cannulated) under local anaesthesia and connected to a FloTrac IQ transducer and haemodynamic data will be displayed on the Hemosphere platform. This monitor will be designated monitor 1. Subsequently, all study sensors will be applied. A Foresight sensor will be placed on the flank, above the kidney (localised by ultrasound) and one on the skin above the quadriceps, at a muscle dense location. Two sensors will be applied to the forehead and will be secured with a headband if necessary. The Foresight sensors will also be connected to the Hemosphere monitor 1. A ClearSight cuff will be placed on a suitable finger on the ipsilateral hand and connected to a second Hemosphere monitor, designated monitor 2. Both monitors will be synchronised for date and time.

A period of ten minutes will be used to capture baseline data before anaesthesia is induced. All treatment will be as per standard institutional care and none of the sensors will be used to guide treatment, except for the FloTrac sensor, which will be used according to routine clinical practice.

All interventions during the procedure including but not limited to fluid therapy, vasoactive drug administration and positional changes will be entered on to the hemosphere platform (monitor 1), and at the end of surgery, all data will be downloaded from each Hemosphere monitor.

Monitor 1 will provide measurements of cardiac output, cardiac index, stroke volume variation, stroke volume, stroke volume index, hypotension probability index, pulse rate, and systolic, diastolic and mean arterial pressure from the invasive arterial waveform and cerebral, renal and muscle tissue oxygen saturations.

Monitor 2 will provide measurements of cardiac output, cardiac index, stroke volume variation, stroke volume, stroke volume index, hypotension probability index, pulse rate, and systolic, diastolic and mean arterial pressure from the non-invasive arterial waveform.

Anonymised versions of all raw waveform data and EMR data will be sent to Edwards Lifesciences for further analyses, including computation of of dP/dT, Eadyn and PPV, and development of predictive algorithms for mapping cerebral desaturations and autoregulation curves from the raw data. Patients' consent for this data transfer to Edwards Lifesciences and outside the EU is obtained as part of the consent process.

6.1 Anaesthetic technique.

Anaesthetic technique will be at the discretion of the anaesthetist as per the current practice at the host institution.

6.2 Discontinuation criteria.

Patients will be withdrawn from the trial

1. Voluntary withdrawal (by patient or consultee).

If subjects are withdrawn from the trial, data collected up to that point will be retained. If the duration of planned surgery is less than the inclusion criteria then an additional subject will be recruited.

6.3 Withdrawal of patients.

In consenting to the trial, patients are consenting to data collection. If a patient wishes to withdraw from the trial prior to surgery they shall be free to do so with no detriment to their medical care

6.4 Blinding.

There is no blinding as this is an observational non interventional study.

7. Regulatory issues.

A notice of no objection from the MHRA is not necessary as the Hemosphere monitor, FloTrac IQ sensor, Clearsight system and Foresight NIRS sensor are all CE marked medical devices being used for their intended purpose. The study also does not require a Clinical Trial Authorisation from the MHRA as it is not a Clinical Trial of an Investigational Medicinal Product.

8. Assessments

8.1 Chart for pre and intra-operative data.

See Case Record File.

8.2 Loss to follow-up.

It is highly unlikely that there will be any loss to follow up as data collection ceases at the end of surgery.

8.3 Trial closure.

The study shall end when the last patient has been has completed surgery.
At the point of study closure the Chief Investigator shall notify the Sponsor in writing that the study has ended. This shall be done in accordance with the York Teaching Hospitals NHS Foundation Trust R and D unit SOP on Trial Closure. Study data will be archived in accordance with the York Teaching Hospitals NHS Foundation Trust and University Medical Centre Groningen SOP

9. Statistical Considerations

9.1 Outcome Measures.

9.1.1 Primary outcome

Data – raw waveform data and their annotations – suitable for development of cerebral and renal autoregulation curves and pilot algorithms to predict cerebral desaturation.

9.1.2 Secondary outcomes

- Agreement between MAP at the upper and lower limits of renal autoregulation from invasive and non-invasive blood pressure measurement.
- Agreement between MAP at upper and lower limits of cerebral autoregulation from invasive and non-invasive blood pressure measurement.
- Agreement between systolic, diastolic and mean arterial pressure derived from invasive and non-invasive measurements.

9.2 Sample Size.

In this study data from 100 patients (50 per site) will be collected for the development of algorithms based on cerebral and renal oxygenation values and (non)invasive blood pressure measurements. Since no such algorithms have been developed

before, an estimate of 100 patients was made to start development and the data collected will power the next stage of development.

9.3 Interim Monitoring and Analyses.

There is no planned interim analysis.

9.4 Analysis Plan.

A full analysis plan will be written prior to data analysis however will include

- Descriptive variables (sex, age, length and bodyweight will be obtained, together with ASA status, medical history, medication use and baseline systolic, diastolic and mean blood pressure), timing and dosing of fluids and vasoactive drugs, surgery specific data (type of surgery, duration, use of epidural analgesia, estimated blood loss) and intraoperative hemodynamic data will be obtained. Continuous data will be presented as means and SD or medians and IQR, depending on the distribution of data. Missing data will be coded as missing and no imputation will be used.
- All intraoperative data will be presented as mean ± sd or as median (IQR) according to their distribution. Missing data will be coded as missing and no imputation will be used.
- Cerebral and renal autoregulation curves will be created using invasive mean arterial pressure as a substitute of cerebral/renal perfusion pressure. Cerebral/renal oxygenation will be used as a surrogate of blood flow.
- Bland-Altman plot will be used to assess agreement and the limits of agreement between both methods
- Multiple linear regression will be used to estimate the effect of demographic variables (age, gender), medical history (diabetes, hypertension, and prior cerebrovascular accident), preoperative blood pressure (MAP, systolic blood pressure, pulse pressure), and time-averaged cerebral oximetry index characteristics on MAP at the LLA.
- Descriptive statistics will be used to present oxygenation data from the quadriceps muscle.

Level of significance

The level of significance will be taken as p< 0.05 and be corrected for repeated measurements

10. Trial Monitoring.

10.1 Clinical site monitoring.

A monitoring plan will be arranged by the Sponsor. Monitoring will take place in accordance with York Teaching Hospitals NHS Foundation Trust's SOPs and will include, at a minimum, a Trial Initiation Monitoring Review, Trial Closure Review and regular visits to monitor CRF accuracy and completeness. An appropriate interval between monitoring visits is to be decided by the Sponsor.

11. Data Protection.

11.1 Direct access to data.

Authorized bodies will have direct access to all study data, including site files and source data, in order to carry out study-related monitoring, audits, ethics committee review and regulatory inspections. Anonymised waveform and annotations data will be sent to Edwards Lifesciences for the development of algorithms and the derivation of certain variables from raw data. Patients' consent for this is obtained as part of the consent process.

11.2 Patient data.

Patients will be allocated a study ID number upon recruitment to the study and all personal identifiers will be removed at the earliest opportunity. Any identifiable information such as contact details or consent forms will be stored in a site file held in a locked filing cabinet. Non-identifiable data will be held on a Trust, password protected computer.

11.3 Confidentiality.

Full medical confidentiality will be maintained in accordance with law in the UK and The Netherlands and the study will be conducted according to GCP guidelines. No patient's name or address will be disclosed to any third party. Patients will not be identifiable in any publication that arises as a result of this study. The study will comply with GDPR.

12. Ethical Considerations and Approval.

12.1 Ethical considerations.

Participants in this study will not have to undergo any additional clinical investigations above and beyond their usual care and will not have to attend any additional hospital appointments.

Full medical confidentiality will be maintained according to UK law for York Teaching Hospitals NHS Foundation and The Netherlands law for University Medical Centre Groningen and the study will be conducted according to GCP guidelines.

The study information and all data will be stored for a period of at least 5 years.

All investigators and research teams will receive training in relevant areas such as GCP, and Standard Operating Procedures (SOPs).

A monitor appointed by the York Teaching Hospitals NHS Foundation Trust will monitor the conduct of the study.

12.2 Ethical approval.

Ethics approval will be sought from an appropriate ethics committee.

12.3 Study withdrawal.

The right of any patient to refuse to participate in the study without giving reasons shall be respected. After the patient has entered the study, all clinicians are free to give alternative treatment to that specified in the protocol, at any stage, if he/she

feels it to be in the best interests of the patient. However, the reason for doing so shall be recorded and the patient will remain within the study for the purpose of data analysis according to the treatment option to which they have been allocated. Similarly, all patients are free to withdraw at any time from the protocol treatment and study follow-up without giving reasons and without prejudicing his/her further treatment.

13. Safety Reporting

All adverse event reporting will be carried out in accordance with the Sponsor's Research Related Adverse Event Reporting Procedures.

For all adverse events, the Clinical Investigator will take appropriate action to ensure the safety of all participants and staff in the study.

13.1 Definition of Adverse Events/Reactions

Adverse Event (AE)

An adverse event is defined as any untoward medical occurrence that occurs to a study participant during the course of the study. Information about adverse events will be collected from the beginning of any study related procedure. For the purpose of this study this is defined as the induction of anaesthesia

For the purpose of this study the adverse events that will be recorded are those that may occur as a result of the sensors applied. Such adverse events will include, but will not be limited to:

- Thermal burns
- Digit ischaemia or injury
- Pain at sensor sites
- Reaction whether due to allergy or otherwise to the sensors
- Any other adverse event deemed relevant by the Chief Investigator.

Serious Adverse Event (SAE)

An adverse event is defined as serious if it results in one of the following:

- Death
- A threat to life

- A new in-patient hospitalisation (not including planned, elective treatment)
- Prolonging of an existing hospitalisation
- Persistent or significant disability or incapacity
- A congenital anomaly or birth defect in a subsequent pregnancy (not expected in this sample of patients)

Serious Adverse Reaction (SAR)

An SAE will be deemed to be an SAR if there is thought to be a possible, probable or definite relationship to the volume of fluid therapy, the use of vasopressors, or the omission of clinically significant treatment. Causality will be rated for all SAEs as follows:

Not related

There is clear alternative explanation for the AE or it has no reasonable temporal relationship to the volume of fluid therapy or use of vasopressors.

Unlikely to be related

The AE may be temporarily linked to volume of fluid therapy or use of vasopressors but is much more likely to be due to other causes.

Possible

The AE has a reasonable temporal relationship with volume of fluid therapy or use of vasopressors but could equally well be explained by these or other causes.

Probable

The adverse event may be due to an alternative cause but it will follow a pattern of a known response and/or a reasonable temporal relationship to volume of fluid therapy or use of vasopressors.

Definitely related

The adverse event cannot be explained by an alternative cause and either follows a pattern of a known response and/or a reasonable temporal relationship to volume of fluid therapy or use of vasopressors

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is an adverse event that is serious, thought to have a possible, probable, or definite relationship to volume of fluid therapy or use of vasopressors and is unexpected.

Expectedness will be rated as:

Unexpected

The nature and/or severity of the event is not consistent with the applicable information about volume of fluid therapy or use of vasopressors.

Expected

The nature and/or severity of the event is consistent with the applicable information about volume of fluid therapy or use of vasopressors.

13.2 Clinical Management of Adverse Events

The supervising clinician will manage any adverse events that should occur. Advice will be provided by the Chief Investigator as necessary. Documentation of any action taken will be recorded in the medical notes and communicated to other relevant parties as necessary.

13.3 AE Follow-up

Adverse events will be followed up by the research team to their conclusion. Follow up of adverse events will cease at hospital discharge or Day 10 whichever is reached first.

13.4 SAE/SUSAR Follow-up

All SAEs or SUSARs will be followed up to their conclusion irrespective of the timeframe of the follow-up period. If necessary this will involve telephone interviews or, if deemed necessary and the study participant is willing, an extra out-patient visit for review by the research team. Any patient discharged home with an ongoing SAE/SUSAR shall be given 24 hour contact details for the research team.

SAE NOTIFICATION

Within 24 hours of becoming aware of anSAE, please fax a completed SAE form to the York Foundation Trust R&D Unit on:

Fax: 01904 725700

14. Financial details

York (50 patients)

Sponsor set up fees 2000 GBP
Chief Investigator time (0.5 PA for 12 months) 6198 GBP
Mid band 4 study co-ordinator 12 079 GBP
Mid Band 7 research nurse 0.2 WTE for 12 months 17 300 GBP
Monitoring 5000 GBP
Archiving 500 GBP
Stationary and consumable 500 GBP

Total 43 577 GBP

Groningen (50 patients)

Research nurse (300 EUR/hr) – 50 patients at 2 hours per patient 30 000EUR
Local project manager (150EUR/hr) – 35 hours 5250 EUR
Overheads at 30% 10 575 EUR

Total 48 825 EUR

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