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ORIGINAL ARTICLE

Clinical implications and feasibility of cerebral autoregulation-based precision blood pressure monitoring in major noncardiac surgery

A protocol for AUTOREGULATE-NONCARDIAC, a multicentre prospective cohort study and peri-operative precision medicine platform

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BACKGROUND Peri-operative hypotension is strongly associated with organ injury following noncardiac surgery, however hypotension avoidance trials have not shown meaningful improvements in cardiovascular outcomes and only inconsistent improvements in renal and neurological outcomes. The true haemodynamic drivers of peri-operative organ injury are probably falls in BP below individual autoregulatory boundaries and not below population-based harm thresholds. Novel methods of personalising peri-operative blood pressure (BP) management are needed. Cerebral autoregulation (cAR)-guided precision BP monitoring is an established paradigm that uses near-infrared spectroscopy (NIRS) to noninvasively estimate the safe BP range for the brain and potentially other vital organs. We aim to assess the feasibility and clinical implications of cAR-based precision BP monitoring in major noncardiac surgery.

OBJECTIVES To investigate the association of intra-operative BP excursions below the lower level of cerebral autoregulation, and other measures of disturbed cerebral autoregulatory function, with the primary and secondary outcomes, to determine the feasibility of cAR-based precision BP monitoring in noncardiac surgery.

DESIGN Multicentre, prospective cohort study.

SETTING 3 Swiss tertiary care centres.

PATIENTS Inclusion criteria: Adults $\geq$45 years of age, at cardiovascular risk, undergoing elective major noncardiac surgery with invasive BP monitoring, surgical time $\geq$90 min, postoperative hospital stay $\geq$1 night. Exclusion criteria include pregnancy, emergency or urological surgery, glomerular filtration rate $<$30 ml min^{-1}, dialysis.

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PRIMARY OUTCOME MEASURES Composite of peri-operative myocardial injury and/or peri-operative acute kidney injury on postoperative days 1 to 3.

SECONDARY OUTCOMES Composite of major cardiovascular, renal and neurological complications up to 1 year following surgery: acute coronary syndrome, acute congestive heart failure, coronary revascularisation, stroke, new or progressive chronic kidney disease, new need for renal replacement therapy, all-cause mortality, cardiovascular mortality.

RESULTS N/A.

CONCLUSIONS N/A.

TRIAL REGISTRATION Association of Intraoperative Blood Pressure Excursions Below Cerebral Autoregulatory Boundaries With Organ Injury Following Major Noncardiac Surgery (AUTOREGULATE-NONCARDIAC), Clinicaltrials.gov NCT05336864. registered 13/04/2022.

KEY POINTS

- Peri-operative hypotension is strongly associated with postoperative complications, however the effectiveness of common hypotension avoidance strategies such as targeting mean arterial pressures >65 mmHg or within 20% of "baseline" values, in preventing postoperative complications has yet to be robustly demonstrated.
- The probable mediators of peri-operative organ injury related to hypotension are falls in blood pressure below the lower limits of autoregulation of vital organs, which may not correlate with population-based blood pressure thresholds or individual "baseline" blood pressures.
- Current consensus statements underline the importance of autoregulation in defining clinically important hypotension and advocate for research into the implications of autoregulation for peri-operative haemodynamic management.
- As a multicentre prospective cohort study and precision medicine platform, AUTOREGULATE-NONCARDIAC will inform future clinical practice and research by investigating the clinical implications and feasibility of cerebral autoregulation-based precision blood pressure monitoring.

Background

Major noncardiac surgery carries a high risk of cardiovascular, renal and neurological complications: 14% to 19% of high-risk patients sustain myocardial injury, 15% to 40% develop kidney injury (AKI) and 7% suffer a covert stroke.[1–6] These sentinel peri-operative events have both short- and long-term prognostic implications.[1,4,6–9] In addition to baseline cardiovascular risk factors, peri-operative hypotension is an important risk factor for postoperative organ injury, including myocardial and kidney injury.[4,10–15] However, targeting peri-operative blood pressure (BP) targets recommended in current guidelines is not associated with clinically meaningful improvements in cardiovascular outcomes and only inconsistent improvements in renal and neurological outcomes following major noncardiac surgery.[2,3,5,16–18]

An explanation for these findings is that the safe BP range during surgery is highly individual and may not correlate with preoperative blood pressures. In cardiac surgery and neurosurgery, the safe BP range for the brain [the cerebral autoregulatory (cAR) range] varies markedly between patients and cannot be reliably predicted using preoperative blood pressures.[19,20] A fall in BP below the lower level of cerebral blood flow autoregulation is not just associated with neurological injury, but also with renal injury and cardiopulmonary complications, suggesting that cAR function could potentially be used as a surrogate for the adequacy of noncerebral vital organ perfusion.[21–25] However, in contrast to other settings, in noncardiac surgery there is a paucity of data on the use of cerebral autoregulation monitoring, specifically of the cerebral oximetry index (COx), a measure of the extent of correlation between changes in near-infrared spectroscopy (NIRS)-derived surrogates of cerebral blood flow and changes in BP, with only small studies having investigated its use and none investigating cardiovascular or renal outcomes.[26–33]

These findings support the investigation of cAR-guided precision BP monitoring as a novel paradigm to personalise and optimise peri-operative haemodynamic status in major noncardiac surgery. With the AUTOREGULATE-NONCARDIAC study (Association of Intraoperative Blood Pressure Excursions Below Cerebral Autoregulatory Boundaries With Organ Injury Following Major Noncardiac Surgery), we aim to prospectively assess the clinical implications and feasibility of cAR-based precision BP monitoring in patients at cardiovascular risk undergoing major noncardiac surgery.

Methods

Ethical considerations

Approval for this study was granted by the Ethics Committee of Northwestern and Central Switzerland (EKNZ 2022-00298) in April 2022. Patient recruitment began in May 2022 using version 1.1 of the protocol. The current version of the protocol is version 1.4, dated 14 April 2025 and forms the basis of this paper. The study is being

conducted in accordance with the study protocol, the Declaration of Helsinki, ICH-GCP, and Swiss legal and regulatory requirements for clinical research. Written informed consent is obtained from each participant before inclusion. Participants may withdraw from the study at any time. If consent is given, any data collected up until then will be used in the analyses. Requests to have collected data removed from the study will be complied with.

Study design

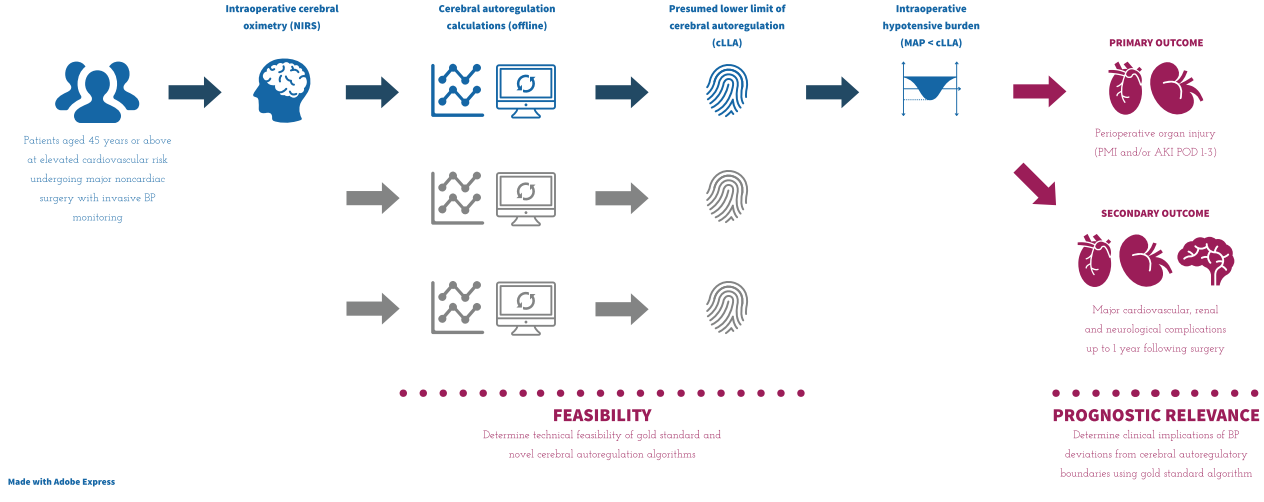
AUTOREGULATE-NONCARDIAC is an investigator-initiated, multicentre prospective cohort study in adult patients at cardiovascular risk undergoing elective major noncardiac surgery (Fig. 1). This study is registered at ClinicalTrials.gov (Identifier: NCT05336864).

Study objectives

As a platform for peri-operative precision medicine research, AUTOREGULATE-NONCARDIAC comprises the following studies and objectives:

(1) **Main intra-operative study (all patients):**
  (a) **Objectives related to primary study outcome**
    (i) **Objective 1 (primary analysis):** To investigate the association of intra-operative blood pressure excursions below the presumed cerebral lower limit of autoregulation (cLLA) with the composite of postoperative organ injury (myocardial injury and/or acute kidney injury) on postoperative days 1 to 3.
    (ii) **Objective 2 (exploratory analyses):** To investigate the association of other measures of disturbed intra-operative cAR with the composite of postoperative organ injury (myocardial injury and/or acute kidney injury) on postoperative days 1 to 3.
  (b) **Objectives related to secondary study outcome:**
    (i) **Objective 3 (primary analysis):** To investigate the association of intra-operative blood pressure excursions below the presumed cerebral lower limit of autoregulation (cLLA) with the composite of major cardiovascular, renal and neurological complications up to 1 year following surgery.
    (ii) **Objective 4 (exploratory analyses):** To investigate the association of other measures of disturbed intra-operative cAR with the composite of major cardiovascular, renal and neurological complications up to 1 year following surgery.
  (c) **Objectives related to haemodynamic data:**
    (i) **Objective 5:** To determine the extent of between-patient variability in the intra-operative boundaries of cAR.
    (ii) **Objective 6:** To determine the extent of within-patient variability in the intra-operative boundaries of cAR.
    (iii) **Objective 7:** To determine to what extent the intra-operative boundaries of cAR can be predicted using preoperative or preinduction blood pressures.
    (iv) **Objective 8:** To determine to what extent within-patient variability in the intra-operative boundaries of cAR can be explained by other intra-operative factors such as CO_2 variability.
  (d) **Objectives related to feasibility:**
    (i) **Objective 9:** To investigate the feasibility of intra-operative cAR monitoring during major

Fig. 1 Summary of main study.



AKI, acute kidney injury; BP, blood pressure; cLLA, cerebral lower limit of autoregulation; MAP, mean arterial pressure; NIRS, near-infrared spectroscopy; PMI, perioperative myocardial injury; POD, postoperative day.

noncardiac surgery based on the success rate of cAR determination, intra-operative uptime, time to first cAR estimate, sensitivity to external factors and sensitivity to data artefacts.

(2) **Neurological injury substudy:**
   (a) **Objective 1 (primary analysis):** To investigate the association of intra-operative blood pressure excursions below the presumed cerebral lower limit of autoregulation (cLLA) with peri-operative neurofilament light trajectories and neurological injury (defined using prespecified delta-NFL thresholds) on postoperative day 2.
   (b) **Objective 2 (exploratory analyses):** To investigate the association of other measures of disturbed intra-operative cAR with peri-operative neurofilament light trajectories and neurological injury (defined using prespecified delta-NFL thresholds) on postoperative day 2.

(3) **Postoperative haemodynamics substudy:**
   (a) In participating centres, patients admitted postoperatively to the intensive care unit will have cAR monitoring continued until postoperative day 1.
   (b) **Objectives related to feasibility:**
      (i) **Objective 1:** To determine the feasibility of postoperative cerebral autoregulation monitoring following major noncardiac surgery.
   (c) **Objectives related to haemodynamic data:**
      (i) **Objective 2:** To determine the extent of between-patient variability in the postoperative boundaries of cAR.
      (ii) **Objective 3:** To determine the extent of within-patient differences between the intra-operative and postoperative boundaries of cAR.
      (iii) **Objective 4:** To determine the extent of within-patient variability in the postoperative boundaries of cAR.
      (iv) **Objective 5:** To determine the extent to which the postoperative boundaries of cAR can be predicted using preoperative or preinduction blood pressures.
      (v) **Objective 6:** To determine the burden of postoperative disturbed cAR.
   (d) **Objectives related to study outcomes:**
      (i) **Objective 7:** To investigate the association of postoperative disturbed cAR function with the Main study primary and secondary outcomes.

(4) **Tissue perfusion substudy:**
   (a) **Objective 1:** To investigate the association of peri-operative trends of peri-operative somatic NIRS (sNIRS) values with surrogates of tissue perfusion derived from routine laboratory analyses (serum lactate).
   (b) **Objective 2:** To investigate the association of peri-operative trends of sNIRS values with the Main study primary and secondary outcomes.

(5) **Processed EEG substudy:**
   (a) **Objective 1:** To investigate the relationship between processed electroencephalogram (pEEG) measures of anaesthetic depth and cAR function (COx).

Study setting

AUTOREGULATE-NONCARDIAC is being conducted at 3 tertiary care centres in Switzerland, with enrolment from 20 May 2022.

Study population

Inclusion criteria:

(1) Adults ≥45 years of age
(2) Undergoing major noncardiac surgery in general anaesthesia, defined as:
   (a) vascular surgery (with the exception of arteriovenous shunt, vein stripping procedures and carotid endarterectomies)
   (b) intraperitoneal surgery
   (c) intrathoracic surgery
   (d) major orthopaedic surgery
(3) At cardiovascular risk, defined as meeting ≥1 of the following six criteria:
   (a) Preoperative NT-proBNP ≥200 ng l^{-1}
   (b) history of coronary artery disease
   (c) history of peripheral vascular disease
   (d) history of stroke
   (e) undergoing major vascular surgery, with the exception of arteriovenous shunt, vein stripping procedures and carotid endarterectomies
   (f) fulfilment of any 3 of the 8 following criteria:
      (i) undergoing major surgery (intrathoracic, intraperitoneal or supra-inguinal vascular surgery)
      (ii) any history of congestive heart failure (CHF) or history of pulmonary oedema
      (iii) anamnestic transient ischaemic attack (TIA)
      (iv) diabetes under treatment with either oral antidiabetic agent or insulin
      (v) age >70 years
      (vi) history of hypertension
      (vii) serum creatinine >175 μmol l^{-1} or calculated creatinine clearance < 60 ml min^{-1} 1.73 m^{-2} (Cockroft Gault)
      (viii) history of smoking within 2 years of surgery
(4) continuous intra-operative invasive blood pressure monitoring indicated due to anaesthetic or surgical factors
(5) planned surgical time ≥90 min
(6) planned postoperative hospital stay ≥1 night

Additional inclusion criteria for neurological injury substudy:

(1) Age ≥65 years

Exclusion criteria:

(1) pregnancy (anamnestic)
(2) emergency surgery
(3) urological surgery
(4) renal insufficiency with creatinine clearance $<30\,ml\,min^{-1}$ (Cockroft–Gault equation) or on dialysis
(5) inclusion in an interventional clinical trial with any common endpoints: acute kidney injury, peri-operative myocardial injury, components of the composite major cardiovascular, renal and neurological complications up to 1 year following surgery (ACS, CHF, coronary revascularisation, stroke, new CKD or progression of CKD, new need for renal replacement therapy, mortality), neurological injury, delirium, exception: inclusion of subset of patients in randomised controlled trial (RCT) investigating the peri-operative use of colchicine in major noncardiac surgery (COLCAT study, NCT06279000).
(6) previously enrolled in this study

Outcomes

Primary outcome

The primary endpoint is peri-operative organ injury on postoperative days (POD) 1 to 3, a composite of:

(1) **Peri-operative myocardial injury (PMI)**, defined as an absolute peri-operative rise in high-sensitivity troponin T (hsTnT) of ≥ 14 ng l^{-1} above preoperative values (or between two postoperative measurements, if preoperative hs-cTnT is missing)
and/or
(2) **Peri-operative acute kidney injury (AKI)**, defined as absolute peri-operative increase in serum creatinine of $>26.4\,\mu mol\ l^{-1}$ or a percentage peri-operative increase in serum creatinine of >50%

Secondary outcomes

Main study (all patients)

Major cardiovascular, renal and neurological complications up to 1 year following surgery, a composite defined as any of the following:

(1) acute coronary syndrome
(2) acute congestive heart failure (CHF)
(3) coronary revascularisation
(4) stroke
(5) new or progressive chronic kidney disease (CKD)
(6) new need for renal replacement therapy (RRT)
(7) all-cause mortality
(8) cardiovascular mortality

Neurological injury substudy (subset of patients)

Peri-operative trajectory (change preoperative/POD2) of serum neurofilament light chain (NFL), a biomarker of axonal injury.

Tissue perfusion substudy (subset of patients)

Surrogates of tissue perfusion derived from routine laboratory analyses (serum lactate); main study primary and secondary outcomes.

Study methodology

Monitoring

In addition to standard peri-operative monitoring, all patients receive bilateral, non-invasive frontal cerebral oximetry monitoring using near-infrared spectroscopy (NIRS) from before anaesthetic induction until the end of surgery. In patients in the Postoperative haemodynamics substudy, this monitoring is continued on the intensive care unit (ICU) until POD1. Patients in the Tissue perfusion substudy additionally get somatic NIRS monitoring on an extremity intra-operatively until POD1. The treatment teams remain blinded to the cerebral and, if applicable, somatic NIRS monitoring, except in the case of a critical desaturation, in which case an alarm would sound.

Data capture

All relevant peri-operative data signals [including invasive arterial blood pressure (ABP), bilateral cerebral NIRS, electrocardiogram, pulse oximetry, capnography and the ventilator] are captured at waveform resolution (with >100 Hz) using the software ICM+ (Cambridge Enterprise, Cambridge, UK). Standard peri-operative clinical monitoring (blood loss, urine output, fluid balance, blood analyses) and therapies (medication and fluid administration, interventions, important surgical events) are captured in institutional electronic health records enabling later data export. All data are captured and exported in de-identified form. The electronic case report forms are stored de-identified in a centralised, encrypted, high-security database accessible only to authorised personnel from participating study sites.

Data processing pipeline

The University Hospital Basel is the Data Coordinating Centre. All data processing takes place offline, following conclusion of all measurements. First, all relevant peri-operative data signals captured with ICM+ undergo both manual and automatic data cleaning to remove artefacts. The cerebral oximetry index (COx), a measure of cerebral autoregulatory function, is calculated as a correlation coefficient between 10 s averages of regional cerebral oxygen saturation (rSO2) and ABP in a window of 5 min and updated every minute.[34] The COx is calculated separately for each frontal lobe. In the next step, all COx data points are grouped into mean arterial BP (MAP) bins of 5 mmHg, ranging from 50 to 150 mmHg. Using the mean COx and MAP values in each bin a second order polynomial is fitted. The minimum of the autoregulatory curve corresponds to cMAPopt, the MAP with optimal cAR function. The MAPs at which this curve transitions from a COx <0.3 to ≥0.3 correspond to the limits of cAR

[lower (cLLA) and upper limits of cerebral autoregulation (cULA)]. Various metrics will be derived and employed to assess the credibility of the obtained autoregulatory curves and estimates for cMAPopt, cLLA and cULA.

Statistical analysis plan

Sample size calculation

Given the lack of previous studies investigating the association of cAR function with peri-operative organ injury in noncardiac surgery, there were scarce data on which to base our sample size calculation. Hence, we powered our study to detect a significant association between the burden of intra-operative hypotension defined using a fixed threshold (MAP < 65 mmHg) and the composite of peri-operative organ injury, assuming this would permit detection of any clinically important association between hypotension defined using personalised BP thresholds (MAP < lower level of cerebral autoregulation) and the composite of peri-operative organ injury. Using data on the incidence of intra-operative hypotension, PMI and peri-operative AKI from a previous trial at one of our study centres, we calculated that a sample size of 319 patients would be required to detect a statistically significant association, at the level of 0.05, between the intra-operative burden of MAP <65 mmHg and the primary endpoint with a power of 80%.[2] Moreover, based on previous, smaller studies on the use of cerebral autoregulation in noncardiac surgery, we additionally accounted for a proportion of patients with nondetectable lower levels of cAR or inconclusive cAR function (COx) curves by increasing the sample size to 500 patients.[26] An interim analysis of the haemodynamic data was planned with the data of the first 200 patients to assess the validity of our assumptions. Based on the observed distribution of haemodynamic data, technical failure rates and study dropout rates, the sample size was increased from 500 to 650 patients.

Planned analyses

For all statistical tests we will consider a two-sided *P*-value <0.05 as statistically significant. In all regression analyses, the influence of continuous predictor variables will be modelled using linear, quadratic or cubic terms, as appropriate. We will report the results of regression analyses using odds ratios or hazard ratios, or as estimates as appropriate, with 95% confidence intervals and the associated *P*-values. Model comparisons will be conducted using the Akaike information criterion and, when appropriate, the Bayes information criterion.

Main study

Objectives 1–4: We will use logistic regression to investigate the association of the intra-operative burden of disturbed cAR function with the primary outcome and Cox regression to investigate the association of the intra-operative burden of disturbed cerebral autoregulatory function with the secondary outcome. The following measures of intra-operative burden of disturbed cAR function will be investigated in separate models: area under threshold (AUT) with MAP < cLLA, area above threshold (AAT) with MAP > cULA, area under/above threshold with either MAP < cLLA or MAP > cULA, area above threshold (AAT) with COx > 0.3, deviation of MAP from cMAPopt. A comparator model will use intra-operative hypotensive burden defined as area of MAP < 65 mmHg as a predictor. All models will be adjusted for age, preoperative hsTnT, Revised Cardiac Risk Index (RCRI) and anaesthetic duration.

Objective 5: The distribution of global intra-operative cAR variables (cLLA, cMAPopt, cULA) will be determined in our study cohort; for each patient all available intra-operative data will be used to generate one global intra-operative estimate of cLLA, cMAPopt and cULA. Descriptive statistics will be derived for cLLA, cMAPopt and cULA in the study cohort.

Objective 6: The *within*-patient, temporal variability of intra-operative cerebral autoregulatory variables (cLLA, cMAPopt, cULA) will be determined in our study cohort. For each patient time trends of cLLA, cMAPopt and cULA will be generated using only the available intra-operative data up to the respective time point, thereby simulating real-time cerebral autoregulation monitoring; the within-patient variability of time trend-based cLLA, cMAPopt and cULA estimates will be calculated. Descriptive statistics will be derived for the calculated measures of *within*-patient variability of cerebral autoregulatory variables.

Objective 7: The relationship between preoperative/pre-induction blood pressures and the intra-operative boundaries of cAR will be explored using correlation and regression approaches.

Objective 8: Potential determinants of *within*-patient variability in the boundaries of cAR will be explored using multivariable regression models.

Objective 9: We will evaluate the following feasibility metrics: success rate of autoregulatory variable (cLLA, cMAPopt, cULA) determination (proportion of patients in study cohort in whom cAR variables can be determined), intra-operative uptime (percentage of intra-operative time during which presumed valid and actionable estimates of cAR variables are delivered), time to first estimate of cAR variables, sensitivity to external factors (changes in gas exchange, administration of vasopressors, skin pigmentation), sensitivity to data artefacts (in BP or rSO_2 signals). Comparisons between the comparator algorithm using the COx methodology (gold standard) and experimental algorithms will be made with regards to technical feasibility and prognostic relevance.

Exploratory analysis 1: Using peri-operative haemodynamic data, haemodynamic phenotypes will be derived, and their prognostic implications investigated. When appropriate, novel modelling techniques will be used (machine learning, deep learning).

Exploratory analysis 2: Further exploratory models will be derived aiming to better characterise the functional relationship between postoperative outcomes and peri-operative haemodynamics, accounting for cAR function, including temporal dependencies.

Neurological injury substudy

Objectives 1 and 2: We will use multivariable linear regression to model the relationship between the intra-operative burden of disturbed cAR function and the peri-operative change in serum NFL. Different measures of the intra-operative burden of disturbed cAR function will be investigated in separate models, in analogy to the Main Study. All models will be adjusted for age, RCRI, anaesthetic duration, anaesthetic type, deep anaesthetic exposure (AUT with low pEEG-derived depth of anaesthesia index), volume of blood transfusions, postoperative ICU admission and peri-operative CRP trajectory. If appropriate, log-transformation of the outcome variables will be performed.

In a separate analysis, different delta NFL cut-offs may be used to define neurological injury as a dichotomous outcome. Logistic regression will be used to assess the association of the intra-operative burden of disturbed cAR function with neurological injury.

Postoperative haemodynamics substudy

Objective 1: The technical feasibility of monitoring cAR function and determining cAR boundaries postoperatively on the ICU will be investigated in analogy to intra-operative monitoring (main study objective 9).

Objective 2: The distribution of global postoperative cAR variables will be determined in analogy to main study objective 5.

Objective 3: The agreement between intra-operatively and postoperatively determined cLLA, cULA and the autoregulatory range will be investigated in patients in whom both intra- and postoperative autoregulation measurements are available.

Objective 4: The *within*-patient, temporal variability of postoperative cAR variables (cLLA, cMAPopt, cULA) will be determined in analogy to main study objective 6.

Objective 5: The relationship between preoperative/pre-induction blood pressures and the postoperative boundaries of cAR will be explored using correlation and regression approaches.

Objective 6: The burden of postoperatively disturbed cAR function will be calculated using both raw COx values (AAT with COx $\geq$ 0.3, time-weighted average (TWA) with COx $\geq$ 0.3), as well as derived estimates of cLLA and cULA (i.e. AUT with MAP $<$ cLLA, TWA with MAP $<$ cLLA resp. AAT with MAP $>$ cULA, TWA with MAP $>$ cULA). Comparisons with the intra-operative burden of disturbed cAR will be drawn.

Objective 7: The association of postoperatively disturbed cAR function, defined using both raw COx values (AAT with COx $\geq$ 0.3, TWA with COx $\geq$ 0.3), and derived estimates of cLLA and cULA (i.e. AUT with MAP $<$ cLLA, TWA with MAP $<$ cLLA resp. AAT with MAP $>$ cULA, TWA with MAP $>$ cULA), with the Main study primary and secondary outcomes will be investigated using logistic regression and Cox regression.

Further substudies

Statistical analysis plans for further substudies will be published online (https://www.pac-network.org/autoregulate-noncardiac).

Missing data

Missing intra-operative data and laboratory data will be omitted from analyses. Sensitivity analyses using multiple imputation will be conducted as appropriate. Patients with incomplete estimates of cAR variables (e.g. cLLA and/or cULA not determinable or not credible based on prespecified criteria), will be included in analyses for which sufficient data are available (e.g. missing cULA will not be considered relevant to analyses relating to cLLA).

Discussion

Rationale

Patients

The study cohort has an elevated risk for peri-operative cardiovascular, renal and neurological complications and is comparable to previous landmark studies.[2,3,7,35,36]

Outcomes

Main study: PMI and AKI are the two complications most strongly associated with intra-operative hypotension.[11] Both are associated with adverse long-term outcomes and are recommended key outcome measures in peri-operative medicine.[1,4,8,37,38] As the predominance of PMI and AKI events occur within the first 3 postoperative days, troponin and creatinine screening is performed on POD1to 3.[2,4,7] The composite outcome major cardiovascular, renal and neurological complications up to 1 year following surgery, is consistent with previous studies on long-term postoperative outcomes and encompasses diseases with high socio-economic burdens, many of which are recommended key outcome measures in peri-operative medicine.[2,3,37–42]

Neurological injury substudy: NFL is a biomarker of neuroaxonal injury with an emerging role in the peri-operative setting. NFL has been shown to rise following surgery, with such increases associated with both delirium and covert stroke following noncardiac surgery.[43–45] Moreover, a peri-operative rise in NFL is associated with cognitive decline at 1 year following cardiac surgery.[46] Current data suggest that NFL peaks between 24 and 48 h following noncardiac surgery with a long half-life, hence the decision to determine NFL on POD2.[43]

Limitations

Although AUTOREGULATE-NONCARDIAC will provide novel data on cAR-based precision BP monitoring in major noncardiac surgery, we anticipate multiple important limitations. First, on a conceptual level, the assumption that cAR boundaries correlate with those of other vital organs – although supported by data from cardiac surgery – may not hold true in this setting or in all patients.[23,25] Moreover, as a pragmatic cohort study, diverse institutions are taking part in recruitment, and clinical management (choice of intravenous vs. volatile anaesthetics, haemodynamic management) is at the discretion of the treatment teams. While this approach increases the generalisability of our results, it may introduce variability that affects cAR function, necessitating appropriate sensitivity analyses. Second, on a technical level, cAR monitoring as employed in this study requires spontaneous haemodynamic variations that challenge cAR function. Hence, in a proportion of patients the boundaries of cAR can only be determined partially or not at all, reducing the power and potentially the generalisability of our analyses. Third, on a methodological level, AUTOREGULATE-NONCARDIAC's findings will be subject to the general limitations of observational studies: residual confounding, bias, and the inability to establish causality.

Potential impact

There is increasing appreciation of the potential limitations of population-based definitions of hypotension.[47–50] Although population-based harm thresholds predict organ injury and postoperative complications on a population level, basing therapeutic interventions on them is not associated with clinically meaningful reductions in the incidence of cardiovascular or renal complications.[2,3,5] Moreover, the clinical impact of targeting preoperative blood pressures and how to best do so remain unclear.[16,17,51] The true haemodynamic drivers of postoperative organ injury are most probably falls in BP below individual, organ-specific autoregulatory boundaries and not falls below population-based harm thresholds.[25,47,50,52] Considering the large variability in autoregulatory ranges in patients in the population and the lacking correlation of these ranges with preoperative BPs, targeting a MAP $\geq$60 to 70 mmHg or within 20% of "baseline" as recommended in current guidelines could expose a substantial proportion of patients to both undertreatment with hypoperfusion of vital organs and overtreatment with excessive vasopressor and fluid administration.[18,19,26]

In line with these data, the most recent Peri-operative Quality Initiative (POQI) international consensus statement on peri-operative arterial pressure management emphasises the central role of autoregulation in defining clinically important hypotension.[50] Specifically, it recommends prioritorising research into key areas: organ-specific hypotensive harm thresholds and the optimal BP to minimise the risk of organ injury, peri-operative factors that may affect harm thresholds, the prognostic implications of different causes of hypotension (i.e. of different hypotension phenotypes), and the optimal choice of vasopressor to protect organs from hypoperfusion.[50]

As a multicentre precision medicine platform, AUTOREGULATE-NONCARDIAC will address these and many other research gaps in peri-operative medicine. In addition to determining the clinical relevance of cAR-based precision BP monitoring in major noncardiac surgery, it will provide data on the feasibility of different approaches to monitoring cAR and will make an important contribution to our understanding of peri-operative haemodynamic phenotypes and of their prognostic implications, informing future clinical practice and research.[49,50,53]

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Conflicts of interest: PMW is collaborating with Covidien/Medtronic in the context of a planned subanalysis of AUTOREGULATE-NONCARDIAC aiming to independently evaluate the Covidien/Medtronic Cotrending algorithm in major noncardiac surgery.

PS receives part of the licensing fees for the multimodal brain monitoring software ICM+, licensed by Cambridge Enterprise Ltd, University of Cambridge, UK.

CH has received research funding from Medtronic and has been a speaker for BD Advanced Patient Monitoring.

CB has received Investigator initiated grant funding from Medtronic (finished 2024).

Dissemination: The results of this study will be presented at international scientific conferences and published in peer-reviewed journals, as well as posted in plain language on the Personalising Acute Care Network website (https://www.pac-network.org/autoregulate-noncardiac).

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Study organisation: Principal investigator: PMW.

Sponsor: LAS.

Local principal investigators: MF, APV.

Supplemental material

Protocol v.1.4 (14 April 2025) (See Supplemental Digital Content 1, http://links.lww.com/EJAIC/A141)

Further information on AUTOREGULATE-NONCARDIAC and all protocol versions can be found on the Personalising Acute Care Network website (https://www.pac-network.org/autoregulate-noncardiac).

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