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PRECISION study: impact of personalised cardiac anaesthesia and cerebral autoregulation on neurological outcomes in patients undergoing cardiac surgery – protocol for an international, multicentre, prospective cohort study

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ABSTRACT

Introduction Adverse neurological complications, including postoperative delirium (POD) and stroke, remain one of the major risks after cardiac surgery. A lack of comprehensive knowledge about their causes and neuroprotective strategies has hindered the development of effective interventions to reduce these events. Personalised cerebral autoregulation (CA)-oriented blood pressure monitoring aims to identify blood pressure targets tailored to each individual patient, thereby reducing brain injury. The PRECISION study aims to assess whether perioperative duration and magnitude of mean arterial pressure (MAP) deviation from an individual's CA limits are associated with adverse neurological complications.

Methods and analysis This international, multicentre, prospective cohort study is conducted at two Swiss and one British hospital. Patients aged 65 years or older undergoing elective primary or re-operative coronary artery bypass graft and/or valvular and/or ascending aorta surgery requiring cardiopulmonary bypass are included. Preoperatively, the patient's baseline of physical, cognitive and mental status is established. Intraoperatively, near-infrared spectroscopy (NIRS) and transcranial Doppler (TCD) are recorded in real-time to generate NIRS-derived and TCD-derived CA indices. The primary endpoint is POD, assessed daily on postoperative days 0 to 7 or up to discharge, whichever occurs earlier with the 3D-Confusion Assessment Method (3D-CAM) or CAM-Intensive Care Unit. Secondary endpoints include a composite neurological outcome of POD and overt stroke, postoperative neurocognitive disorders, major morbidity and mortality. Associations between neurologic outcomes, neurobiomarkers and genetic variation will be explored. A total of 500 participants is required to achieve 90% power to find a statistically significant effect of the area under the curve MAP<lower limit of CA (LLA) on the risk of POD at the 5% level. This includes adjustment for potential confounders and for the inability to determine the LLA.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This international, multicentre, prospective cohort study will collect high-quality data on cerebral autoregulation throughout the entire perioperative period in patients undergoing cardiac surgery.
- ⇒ This interdisciplinary study will contribute to aetiological research by establishing biological associations between adverse neurological complications, brain injury biomarkers and genetic variation, as complementary strategies to further clarify the pathophysiological mechanisms.
- ⇒ This properly powered study fills a gap by providing a reliable clinical characterisation of the cardiac surgery population across three tertiary hospitals in Europe, while investigating whether a higher burden of cerebral haemodynamic insults is associated with adverse neurological complications.
- ⇒ The comprehensive methodological approach is well-suited to assess feasibility and further develop non-invasive methodologies using near-infrared spectroscopy and transcranial Doppler to derive personalised blood pressure targets.
- ⇒ Although this study is observational in nature, which limits causal inferences, broad inclusion criteria and a representative sample size will increase the external validity of our findings.

Ethics and dissemination Ethical approval has been obtained from all responsible ethics committees (Swiss lead ethics committee EKNZ 2022-01457 and Health Research Authority and Health and Care Research Wales, UK, REC 23/SW/0076). Results will be disseminated at national and international conferences and published in peer-reviewed journals.
Trial registration number NCT05595954.

INTRODUCTION

Background

Adverse neurological complications remain one of the major risks after cardiac surgery. In line with the demographic shift in ageing, the number of high-risk patients and complex procedures has steadily risen over time.[1 2] Despite the decrease in mortality over the last decades,[3] the burden of neurological morbidity after cardiac surgery remains high and places enormous pressure on already over-stretched healthcare systems.[4]

The most common neurological complication after cardiac surgery is postoperative delirium (POD), with an incidence of up to 52%.[5] POD was made a priority by the American Society of Anesthesiologists due to its multifactorial impact,[4] and in 2021 an expert consensus to reduce the incidence of postoperative neurocognitive disorders (PNCD) was issued.[6] Notably, the occurrence of POD during hospitalisation increases the risk for neurocognitive decline over time,[7–9] loss of instrumental activities of daily living,[10–13] dementia and doubles a patient's risk of being institutionalised after discharge.[7 14 15] Moreover, POD has been significantly associated with prolonged length of hospital and intensive care unit (ICU) stay, hospital readmission, increased healthcare costs[16 17] and mortality.[15–17] Perioperative stroke is a further devastating neurological complication, also associated with cognitive decline, prolonged length of hospital stay and higher morbidity,[18] and recent data suggest that its occurrence may be increasing.[19]

Rationale and evidence gap

A lack of a comprehensive knowledge of the causes of adverse neurological complications after cardiac surgery[20] has prevented the development of strategies to effectively reduce these outcomes. However, the perioperative anaesthetic management of cardiac surgical patients presents possibilities to address this question.

Evidence for optimal perioperative blood pressure (BP) targets that consider the high interindividual variability of cerebral autoregulation (CA) limits[21 22] is lacking. Currently, it is not possible to recommend a range of BP values that should be maintained perioperatively to prevent harm to the brain based on population-derived thresholds.[23–25] However, personalising the definition of optimal mean arterial pressure (MAP_{opt}) with CA limits when managing patients under anaesthesia to preserve cerebral perfusion pressure (CPP) might avoid cerebral hypo- and hyperperfusion, thus reducing the risk of secondary brain injury.[26] CA can be assessed clinically at the bedside by measuring cerebral blood flow (CBF) changes or its surrogates in relation to CPP.[27 28] Two non-invasive methods for calculating CA in the clinical setting include near-infrared spectroscopy (NIRS) and transcranial Doppler (TCD). The first single-centre randomised controlled trial (RCT) to use MAP_{opt} during cardiopulmonary bypass (CPB) in cardiac surgery showed promising results, with a marked reduction in POD in patients who received MAP_{opt}-oriented therapy.[29] However, a second RCT using an identical approach found no statistically significant differences in a complex composite outcome of clinical stroke, neurocognitive dysfunction and brain imaging lesions. Importantly, this trial faced some feasibility issues and was stopped for futility of the intervention.[30] Hence, the promising results shown by the first RCT to use MAP_{opt} during CPB in cardiac surgery[29] and the challenges faced by the second RCT[30] lend strong support to further research.

Study aim

This international, multicentre, prospective cohort study will take three approaches. First, non-invasive, personalised CA-oriented BP monitoring will assess whether perioperative duration and magnitude of MAP outside of an individual's CA limits using NIRS and TCD are associated with adverse neurological complications by establishing tailored BP targets.[31] The primary objective is to investigate whether patients with a higher burden of cerebral haemodynamic insults, defined by the duration and magnitude spent outside of an individual's CA limits or deviation from MAP_{opt} are associated with the incidence and severity of POD, have an increased incidence of adverse neurological complications or have poorer neurological outcomes. In parallel, establishing biological associations between adverse neurological outcomes, brain injury biomarkers and genetic variation is a complementary strategy to further clarify the pathophysiological mechanisms and consequences of perioperative neurological complications that may move us to a proactive patient-tailored paradigm, ultimately improving outcomes, patient safety and quality of life.

METHODS AND ANALYSIS

Study design

This international, multicentre, prospective cohort study is being conducted at the University Hospital Basel (Switzerland), Royal Papworth Hospital (Cambridge, UK) and Bern University Hospital (Switzerland). This study aims to recruit 500 patients undergoing cardiac surgery.

Population, eligibility and consent

This study is being conducted in patients aged 65 years or older, a population at higher risk of adverse neurological complications. Eligible patients are approached by telephone and provided with the patient information sheet via email/post or during the preoperative anaesthesia visit. Written informed consent is being obtained from all participants before performing the baseline cognitive assessment.

Inclusion criteria

- Age ≥65 years;
- Undergoing elective primary or reoperative coronary artery bypass graft and/or valvular and/or ascending aorta surgery requiring CPB.

Exclusion criteria

- Surgery requiring moderate (28°C–31.9°C) or deep (<28°C) hypothermic circulatory arrest[32 33];
- Heart and/or lung transplantation;
- Urgent (within 24 hours) and emergency surgery;
- Inability to follow procedures or insufficient knowledge in English, German or French;
- Inability to give consent.

Patient and public involvement

Patients and members of the public were involved at several stages of the study in the UK, including the design and conduct of the study. The burden of the research visits on patients was carefully assessed. The Royal Papworth Hospital Patient and Public Involvement (PPI) panel extensively reviewed and provided feedback on patient-facing documentation and study synopsis. Dissemination of the main results to study participants is planned and will follow the method deemed most appropriate by the PPI panel.

Study procedures

The project is expected to be completed within 4.5 years, with a 42-month recruitment period and a 1-year follow-up after enrolment. Recruitment began in March 2023 and is planned to close in August 2026. The study is expected to be completed in July 2027. A study overview is provided in figure 1.

Preoperative period

Preoperative evaluation, risk stratification and individual patient optimisation are being performed according to institutional standard practice and implemented guidelines. Preoperatively, patients are assessed using the 3 min Diagnostic interview for Confusion Assessment Method-defined delirium (3D-CAM), the modified National Institutes of Health Stroke scale (mNIHSS), the Montreal Cognitive Assessment (MoCA V.8.1), the Geriatric Depression Scale (GDS), the Clinical Frailty Scale, and hand grip strength measurement (using a hand dynamometer) by trained study personnel to establish a baseline assessment of the physical, cognitive and mental status.

Intraoperative period

Intraoperatively, invasive arterial BP monitoring is installed before induction. NIRS monitoring (INVOS, Medtronic, Ireland or O3, Masimo, Irvine, California, USA) is started using two sensors placed bilaterally on the forehead. Several clinical studies have found that NIRS' rSO_2 signals might be a clinically appropriate surrogate of CBF for CA monitoring,[28 34 35] as rSO_2 is directly related to MAP. The NIRS-derived cerebral oximetry index (COx)[36] and haemoglobin volume index (HVx, a vascular reactivity index calculated from relative total haemoglobin)[37 38] will be calculated separately for each cerebral hemisphere as a moving Pearson correlation coefficient between 30 consecutive time-averaged values of arterial BP and rSO_2 over 10 s, updated every minute. Subsequently, the CA indices will be Fisher-transformed, and all data points will be grouped into MAP bins of 5 mm Hg and, for each bin, mean COx/HVx and MAP values will be used to fit a second order polynomial describing the theoretical U-shape autoregulatory curve. When BP is

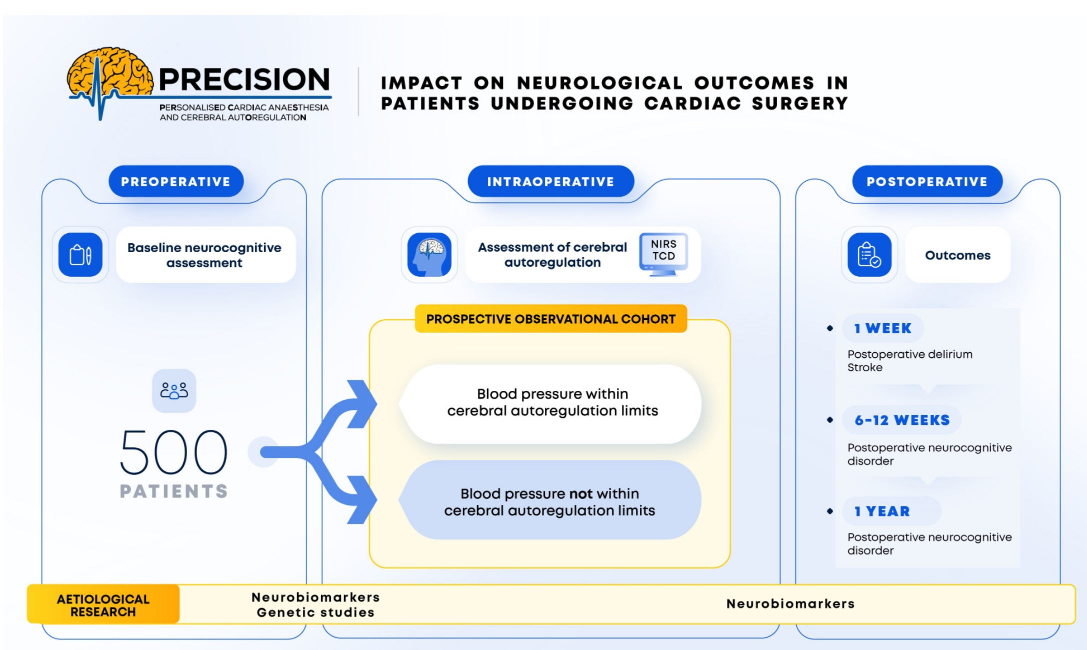

Figure 1 Study overview. NIRS, near-infrared spectroscopy; TCD, transcranial Doppler.

within the autoregulation limits, CBF is independent of changes in MAP; there is no correlation between MAP and CBF, and either COx or HVx approaches zero. However, when BP is outside the autoregulation thresholds, COx or HVx approaches one, indicating MAP-dependent passive cerebral perfusion (common threshold <0.3–0.35). COx and HVx have been validated against a number of established methods[28 34 37] and offer the ability to evaluate, monitor and predict the limits of CA and its disturbance perioperatively. The MAP at the lowest turning point of the obtained CA curve will be defined as the MAP_{opt}. Different thresholds for COx and HVx to define impaired CA will be assessed, and the interception of such cut-off values on the left and right sides of the U-shape curve will represent the lower (LLA) and the upper (ULA) limits of CA, respectively. Curve fitting criteria will be applied to assess the quality of the obtained CA curves and estimates for MAP_{opt}, LLA and ULA.

In a next step, anaesthesia induction starts and anaesthetics are given according to institutional practice and consist of propofol/midazolam, fentanyl/sufentanil/remifentanil, rocuronium or atracurium and sevoflurane/isoflurane. Inhalational anaesthetic concentrations are administered according to the routinely used depth of anaesthesia monitoring. Before or after anaesthesia induction, continuous CBF measurement in both middle cerebral arteries (MCA) using TCD monitoring (DWL, Compumedics DWL, El Paso, Texas, USA) is started, whenever logistically possible, using two 2 MHz probes positioned over the transtemporal window. TCD-derived indices will serve as a quality metric of CA and allow comparison with NIRS-derived indices. TCD is a non-invasive validated method to continuously monitor CBF velocity and assess CA,[39 40] assuming that minimal changes in the diameter of the MCA occur with spontaneous changes in MAP.[41] Similar to COx and HVx, the mean velocity index (Mx) is a moving correlation coefficient that can be calculated between low-frequency (≤0.05 Hz) changes in CBF velocity and MAP or CPP.[27] When Mx approaches zero, CBF is constant despite changes in MAP or CPP and CA is preserved (common threshold <0.4). Monitoring autoregulation using TCD in patients undergoing cardiac surgery has been successfully validated before,[34 42] allowing spontaneous fluctuations in MAP to be used to characterise CA. Nevertheless, movement artefacts, electrocautery or an inadequate transcranial acoustic window limit TCD use. Pragmatically, in all patients with no acoustic window, TCD monitoring will be discontinued. NIRS and TCD monitoring technologies of CA have been developed, validated and applied successfully by several members of our group.[28 33 38 39 43–46] The intraoperative data, including invasive arterial BP, heart rate, end-tidal/arterial/transcutaneous CO_2, digital rSO_2 and TCD signals, are collected and recorded in real-time and are transferred directly to a research laptop, which is interfaced with the haemodynamic and depth of anaesthesia monitors and ventilator. The data is collected in real-time and recorded using the ICM+ research software (Cambridge University; Cambridge, UK). Depth of anaesthesia and electroencephalogram parameters are monitored using either Bispectral Index (Medtronic, Dublin, Ireland) or SedLine (Masimo).

NIRS is not a standard anaesthetic monitoring for all patients undergoing cardiac surgery in all participating centres. In such cases, the care team will be blinded to the NIRS measurements, precluding any systematic effect. Perioperative care, including administration of catecholamines and volume management, will be provided and documented according to usual institutional clinical practice at the discretion of the anaesthetist or perfusionist in charge. Normocapnia will be maintained according to arterial blood gas analyses performed as part of standard clinical practice. During CPB, alpha-stat acid-base regulation will be used.

Postoperative period

Since signs of significant CA dysfunction continue into the early postoperative period,[47] NIRS and depth of anaesthesia monitoring will be continued in the ICU after the surgery until (1) endotracheal extubation or (2) for the first 24 hours or (3) until emergency re-operation, whichever occurs first. Afterwards, neuromonitoring is discontinued, and the data collected is saved in the research laptop. Postoperative care is provided per institutional standard. Trained study personnel evaluate participants for POD with 3D-CAM/CAM-ICU and for clinical stroke with mNIHSS daily on postoperative days 0 to 7 (or until hospital discharge, whichever occurs first). CAM-ICU includes the Richmond Agitation Sedation Scale assessment,[48] in which a score of –4 or –5 indicates coma and does not allow further CAM-ICU testing. Follow-up visits twice daily or after day 7 are necessary in some instances (eg, if neurological symptoms fluctuate, occur de novo or extend beyond day 7). Further PNCD is assessed using GDS and MoCA (or MoCA-Blind,[49] if done remotely by telephone) and established by comparing its results with the patient's baseline.[50 51] These tests will be performed in two follow-ups, which can be performed on-site or remotely between 6 and 12 weeks and up to 12 months after surgery. Cognitive impairment will be defined as a decline in performance from baseline to postoperative testing of 1–2 SDs (mild PNCD) or ≥2 below norms (major PNCD).[6] Values will be corrected by age, sex and education,[52] and results for each MoCA domain will also be specified.

Brain injury serum biomarkers and genetic studies

The planned serum biomarker panel includes four markers of neurological injury (glial fibrillary acidic protein (GFAP), neurofilament light (NfL), total tau (t-tau) and ubiquitin-C-terminal-hydrolase-L1 (UCH-L1)).[53] However, the final choice of the analysis platform (such as the Simoa Human Neurology 4-Plex assay, Quanterix, Lexington, Massachusetts, USA) and any additional analyses (eg, pTau217) will be determined after recruitment terminates, depending on the available technology. Blood samples are obtained preoperatively, on the day of surgery after ICU admission, on postoperative days 1, 2, 6 (or hospital discharge, whichever occurs first) and between 6 and 12 weeks after surgery. The blood samples are collected in vacutainer tubes and centrifuged at 2000xg for 10 min at room temperature within 1 hour. Successively, 500 µL serum aliquots are pipetted into Eppendorf tubes and stored at −80°C within 2 hours. Regarding genetic studies, the procedures already employed by our research group will be implemented.[54] DNA will be extracted from a whole blood sample obtained preoperatively using a commercially available kit according to the manufacturer's protocol. Genotyping will be performed using the Infinium Global Screening Array with multi-disease drop on a fully automated iScan System (Illumina, San Diego, California, USA). Quality-control parameters for genotype will be implemented. Subsequently, the resulting single nucleotide polymorphisms will undergo analysis. An additional candidate gene analysis will be performed to address the cumulative impact of several markers in a gene that have moderate effects on the phenotype.

Objectives and endpoints

The primary objective of this study is to assess the relationship between time and deviation of MAP from CA thresholds and adverse neurological events. This concept of hypotensive or hypertensive load assumes that a minor but prolonged hypotensive or hypertensive episode, respectively, may have an equally deleterious impact as a major, although brief, period. Therefore, we aim to investigate whether patients with a higher burden of cerebral haemodynamic insults, defined by the duration and magnitude spent below the LLA or above the ULA, have an increased incidence of adverse neurological events or have poorer neurological outcomes, namely POD, PNCD and clinical stroke.

The primary endpoint of this study is POD assessed daily on postoperative days 0 to 7 (or up to discharge, whichever occurs earlier) with the 3D-CAM[19] or CAM-ICU.[55] The secondary endpoints are:

- Composite neurological outcome on postoperative days 0 to 7 (or discharge, whichever occurs earlier) of POD and/or clinical (overt) stroke, assessed daily with the mNIHSS and confirmed by brain imaging.[56–58]
- PNCD, assessed with MoCA between 6 weeks and 12 weeks, and up to 12 months after surgery.
- Brain injury serum biomarkers (GFAP, NfL, t-tau and UCH-L1) concentrations measured perioperatively and their association with the burden of cerebral haemodynamic insults and incidence of adverse neurological outcomes, namely POD, PNCD and clinical stroke.
- Acute kidney injury, defined as a postoperative increase in serum creatinine of ≥26.5 µmol/L (≥0.3 mg/dL) within 48 hours or ≥1.5 times baseline values.[18 59]
- De novo renal replacement therapy after surgery up to discharge.
- Major morbidity, as defined by the Society of Thoracic Surgeons, as having at least one of the following adverse outcomes: stroke, surgical re-exploration for any cardiac reason (bleeding, coronary graft occlusion, valve dysfunction), renal failure, deep sternal wound infection/mediastinitis and prolonged ventilation (>24 hours).[60]
- Depth of anaesthesia and electroencephalographic burst-suppression.
- Length of ICU (in hours) and hospital (in days) stay.
- Perioperative mortality, defined as any in-hospital or postdischarge death within 30 days after surgery, regardless of cause, or any death occurring during the hospitalisation, even after 30 days,[61] and 1-year mortality.

Additional secondary objectives of this study are the:

- Determination of the number of patients with available LLA, ULA and MAP_{opt}, and the time required to achieve the first calculated value of LLA, ULA and MAP_{opt} using the different CA metrics;
- Comparison of sensitivity of LLA, ULA and MAP_{opt} to clinically adverse outcomes;
- Exploration, comparison and agreement between the different CA metrics;
- Determination of the incidence and delineation of the temporal pattern (preoperative, during/after CPB, postoperative) of CA dysfunction, defining the most at-risk period perioperatively, and allowing evaluation of the value of extending the monitoring period to the postoperative period;
- Exploration of the relationship and temporal patterns between recorded perioperative real MAP and calculated MAP_{opt};
- Assessment of the feasibility of continuous CA monitoring postoperatively in the ICU;
- Exploration of the association between spectral patterns of electroencephalography (EEG), depth of anaesthesia, POD and CA;
- Evaluation of TCD-based clinical assessments for CA during routine steps of cardiac surgery and comparison and agreement with the different CA metrics;
- Exploration of the agreement between arterial, end-tidal and transcutaneous carbon dioxide measurements and its impact on CA;
- Association between the width of an individual's CA plateau (ULA minus LLA) and brain injury serum biomarkers;
- Exploration of the association between higher burden of cerebral haemodynamic insults and lengths of ICU and hospital stay, heart rate variability, baroreflex sensitivity, frailty and clinical outcomes.

Sample size calculation

The most important study providing some results relating to potential effects of the area under the curve (AUC) MAP below the LLA (AUC MAP<LLA) on the incidence of POD is an RCT that compared MAP targets according to institutional practice with a group where the MAP was

attempted to be kept above LLA[62] This study reported an incidence of POD of 39/103 (≈37.9%) in the intervention group and of 48/91 (≈52.7%) in the control group. The quartiles of AUC MAP<LLA were 2.0, 5.3 and 13.4 in the intervention group and 3.7, 9.5 and 19.5 in the control group.

Fitting gamma distributions to these quartiles provided parameters alpha=0.63 and beta=0.063 for the intervention group and alpha=0.93 and beta=0.066 for the control group. The corresponding mean values and SD were 10.0 and 12.6 for the intervention group and 14.1 and 14.6 for the control group.

Assuming a linear relationship between logit(incidence) and AUC MAP<LLA, we can get a tentative estimate of the coefficient of AUC MAP<LLA in the logistic function of POD incidence as a function of AUC MAP<LLA, by dividing log(48/91/39*103) by the difference in the means of AUC MAP<LLA between the two groups (ie, 14.1–10.0=4.1). The corresponding value is 0.078.

For our study, we assumed a POD incidence of 0.4 according to our data.[62] With the parameters $\gamma 0=-1.49$ and $\gamma 1=0.078$, we obtained

$$\int_0^{\infty} f_{CON}{}^{(x)}\, g^{(x)} = 0.4^{(*)}$$

Thus, a power simulation with these parameters for the gamma distribution of the control group was performed and found that a sample size of 60 patients would provide more than 90% power for finding a statistically significant effect of AUC MAP<LLA at the 5% level. The corresponding estimates of POD incidence at the lower and upper quartiles of the gamma distribution in the control group would be 23% and 51%, respectively, which seemed to be an unrealistically large difference. With $\gamma 1=0.03$, we would obtain $\gamma 0=-0.85$, to preserve (*). The corresponding incidence estimates for the lower and upper quartiles would then be 31.5% and 43.4%, respectively. Under these assumptions, we would achieve 90% power with a sample size of 250. Taking this as a reference point, we plan for a sample size of 500. This is to accommodate the loss of power occurring due to the adjustment for potential confounders and for the inability to determine LLA in an estimated fifth of patients.

Statistical analysis

Baseline characteristics will be descriptively compared between patients with and without POD.

Primary analyses

- Association of POD with duration and magnitude of MAP below the LLA (AUC MAP<LLA).
- Association of POD with duration and magnitude of MAP outside of the individual's CA limits (AUC MAP<LLA and AUC MAP>ULA).

Secondary and sensitivity analyses

The association of the following endpoints with duration and magnitude of MAP below the LLA and outside of the individual's CA will be assessed: composite outcome of POD and/or clinical stroke, PNCD and major postoperative morbidity. The corresponding associations will be assessed using logistic regression models adjusted for potential confounding variables according to figure 2 (see also online supplemental file). Patients with MAP_{opt} will be equally assessed as follows: AUC MAP<MAP_{opt} for all patients with LLA and MAP_{opt}. In a sensitivity analysis, patients without LLA will also be included using MAP_{opt}

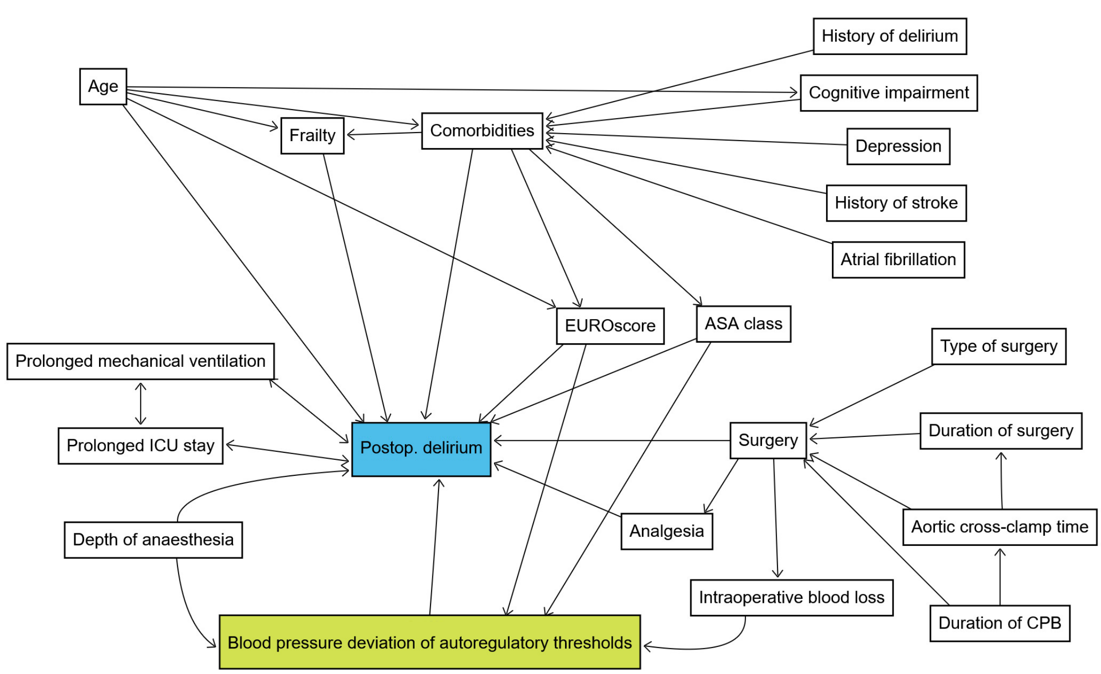

Figure 2 Directed acyclic graph of postoperative delirium. ASA, American Society of Anesthesiologists; CPB, cardiopulmonary bypass; ICU, intensive care unit.

as follows: AUC MAP<MAP$_{opt}$ only for the patients without LLA. Patients without LLA and without MAP$_{opt}$ will be excluded from main statistical analyses. For all analyses, a $p<0.05$ will be considered statistically significant.

In addition, the percentage of time spent in risk regions (ie, the duration of MAP below the MAP$_{opt}$, below the LLA and above the ULA) will be explored as further parameters to quantify the relationship between MAP, CA and outcomes. Three-dimensional visualisation methods ('heat maps') will be used to depict the impact of MAP duration and magnitude on all relevant outcomes.

Subgroup analysis

We will graphically investigate the group differences in primary as well as secondary endpoints across participants who have received benzodiazepines and the ones who did not, across the groups for temperature of CPB (ie, normothermia (≥35°C), mild hypothermia (32°C–34.9°C)) and across the groups for complexity of the surgical procedure (ie, isolated coronary artery bypass graft, valve surgery, aorta surgery, combined procedures).

Exploratory analyses

- The primary endpoint will additionally be explored using the alternative outcome of delirium-free days. (Log-) linear regression with robust variance estimates might be used for this purpose.
- The association between postoperative adverse neurological outcomes (clinical outcomes) and elevated concentrations of brain injury serum biomarkers will be explored using linear regression models with robust variance estimates. For some biomarkers, a log-transformation may be warranted. In addition, the association between AUC MAP<LLA (and MAP>ULA) and biomarkers will be explored using (log-) linear regression with robust variance estimates. Consistency in the findings of these exploratory analyses will be interpreted as supporting evidence of our study hypotheses.
- The associations between being outside of CA and various novel EEG markers, such as specific spectral burst signatures, aperiodic slope limits and various complexity (entropic) measures, and the relationships between these markers and subsequent postoperative adverse neurological clinical outcomes.
- The effect of the temperature on CA will be further explored in participants with unplanned or urgent intraoperative moderate or deep hypothermic circulatory arrest.
- A genome-wide association study will be conducted to identify potential genetic variations or candidate genes conferring an increased risk for brain injury in adults undergoing cardiac surgery.
- All prespecified objectives will be analysed in an explorative way using tables, graphs and heat maps.

This research plan will follow the reporting guideline Strengthening the Reporting of Observational Studies in Epidemiology.[63] The analysis will be performed using Stata V.18 or higher (StataCorp) or R V.4.4.2 or higher (R Core Team, Vienna, Austria).

Data collection and management

A web-based electronic database is used for data entry. The intraoperative parameters collected in real-time will be visually assessed and classified by the research team according to their quality. Signals of individual high-resolution recordings will then undergo offline data cleaning and processing before statistical analysis. BP measurement artefacts will be removed manually and automatically. Recordings with unreliable or unavailable values of BP and rSO_2 signals, and low or unstable amplitude of BP signals will be classified as poor quality data and will be excluded from the analysis. CA indices and limits, and MAP$_{opt}$ will be calculated as described above. Whenever different LLA and/or ULA are calculated from the left and the right digital rSO_2 signals, the higher limit for the LLA and the lower limit for the ULA will be selected for analysis. Alternative and experimental autoregulation algorithms, such as the expanding window approach and time series modelling, will be tested in exploratory analyses by our group, which has pioneered this technology.[28 43 64]

ETHICS AND DISSEMINATION

This study has been approved by the ethics committees of all centres (Swiss lead ethics committee: Ethikkommission Nordwest- und Zentralschweiz (EKNZ) 2022-01457; and Health Research Authority and Health and Care Research Wales, IRAS project ID 322179, REC reference 23/SW/0076). The study has been registered at ClinicalTrials.gov (NCT05595954, 18 October 2022).

Considering the high incidence of adverse neurological events following cardiac surgery, the well-established association between BP and morbidity and mortality, the known inadequacy of population-based BP cut-offs in individual patients to protect the brain, and the unmet need for adequately individualised BP ranges using non-invasive monitoring according to the individual's autoregulatory status, this project is of high clinical and scientific relevance with the potential of high impact on patient outcomes. The chosen study population is in line with other landmark studies in perioperative medicine, and perioperative management will be consistent with current guidelines[65] ensuring the generalisability of study findings.

Biological material (non-genetic and genetic) is deidentified and appropriately stored in the participating hospital laboratories and certified biobanks only accessible to authorised personnel and in accordance with technical guidelines of each laboratory and biobank, assuring their integrity and security. Data, including blood samples collected as part of this study, may be transferred between the participating centres for further analysis and may be shared with other biomedical researchers conducting ethically approved studies, including those from non-EU countries involved in medical research, that comply with the same standards as in Switzerland and United Kingdom. In addition, data and samples generated by the study may be analysed by commercial collaborators (such as those involved in developing new medicines or diagnostic devices) based either in Switzerland, the UK or overseas. Regarding genetic studies, participants may opt to consent to biological material analyses except for genetic analyses. Two additional blood samplings are taken postoperatively and stored so that they can be used for future genetic research projects that have not yet been defined and for which ethical approval will be attained. Remaining biological materials will be stored in biobanks in accordance with local technical and legal standards for 10 years after publication of this study for future research projects that have not yet been defined in more detail and for which an ethical approval will be attained.

The results of this project will be presented at international scientific conferences and published in peer-reviewed journals.

The current study protocol is v1.4 dated 8 August 2025.

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