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Predicting Gastrointestinal Complications After Cardiac Surgery From Mean Arterial Blood Pressure Under a Data-Driven Threshold for Hypotension: Protocol for an Advanced Database Study

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ABSTRACT

Background: Hypotension during cardiopulmonary bypass may increase the risk of gastrointestinal complications due to insufficient splanchnic autoregulatory capacity. We hypothesize that both duration and level of blood pressure below a data-driven threshold during cardiopulmonary bypass are associated with the risk of gastrointestinal complications.

Methods: Patients who underwent cardiac surgery at Copenhagen University Hospital, Rigshospitalet, during 2018–2022 will be included if they underwent on-pump valve surgery, coronary artery bypass grafting, and/or surgery on the ascending aorta. The primary outcome is major gastrointestinal complications within 30 days, defined as acute intestinal ischemia, abdominal surgery, bowel perforation, or gastrointestinal hemorrhage. Secondary endpoints are serious gastrointestinal complications, delayed recovery of bowel function, cholinesterase inhibitor administration, and 30-day mortality. The exposure is the exposure to lower blood pressure, calculated as the product of the duration and level of blood pressure below a data-driven threshold. To identify the optimal threshold, we split the population in a training (75%) and validation cohort (25%). In the training cohort we will identify the threshold with the highest area under the receiver operating curve for the primary outcome. The selected threshold will then be applied to quantify the exposure to lower blood pressure for each patient. Patients will be grouped using a modified Youden's index (weighing sensitivity 80%) as a cutoff for high versus low exposure to lower blood pressure, and association with the study endpoints will be determined in the validation cohort.

Conclusion: Under the assumption of pressure-dependent perfusion outside of an autoregulatory plateau, the exposure to blood pressure below a threshold might reflect the risk of gastrointestinal complications more accurately than point measures or averages. The results from this study may lead to relevant hypotheses for prospective testing.

Bo Laksáfoss Holbek reports consultancy agreement with Medtronic, and speaker's fee from Medela.

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1 | Introduction

Complications from the gastrointestinal tract occur approximately after 3.5% of cardiac surgeries and are associated with high mortality (14%) [1]. While no definitive evidence exists, splanchnic hypoperfusion has been suggested as one potential driver of gastrointestinal complications from on-pump cardiac surgery [2].

The intestinal mucosa is routinely exposed to subclinical ischemic injury during cardiopulmonary bypass, resulting in weakened barrier function, bacterial translocation, and endotoxemia [3–5]. Intestinal mucosal ischemia measured by serum diamine oxidase activity indicates progressive ischemia throughout cardiopulmonary bypass—a pattern not found in off-pump coronary artery bypass grafting [3]. It is therefore relevant to investigate features of cardiopulmonary bypass, such as hypotension from vasoplegia [6], in relation to hypothesized ischemia-associated gastrointestinal complications.

End-organ blood flow is normally maintained at a stable rate despite fluctuations in blood pressure by autoregulation of local flow, however only within an organ-specific blood pressure range after which arterioles reach maximal dilatation and flow becomes pressure-dependent [7]. Theoretically, a lower mean arterial blood pressure (MAP) could consequently compromise splanchnic blood flow during cardiopulmonary bypass despite a constant and adequate systemic blood flow. Raising MAP during cardiopulmonary bypass by infusion of adrenergic drugs may however also reduce splanchnic blood flow from alpha-adrenergic mediated vasoconstriction [8]. As flow is proportional to the vessel radius to the power of four (Poiseuille's law) [9] even minimal splanchnic arteriolar constriction may significantly reduce flow.

An optimal MAP balancing autoregulation and drug-mediated splanchnic vasoconstriction during cardiopulmonary bypass may exist; however, the current guideline recommendation on MAP during cardiopulmonary bypass does not include evidence on gastrointestinal complications [10].

Therefore, this study will use a data-driven algorithm to define a gastrointestinal-specific threshold for hypotension during cardiopulmonary bypass and assess if the product of the duration and magnitude of exposure to mean arterial blood pressure below this threshold is associated with increased odds of gastrointestinal complications.

2 | Methods

This is a retrospective cohort study of cardiac surgeries performed in the Department of Cardiothoracic Surgery, Copenhagen University Hospital—Rigshospitalet. The study will adhere to the Helsinki Declaration and is approved by the Ethics Committee of the Capital Region of Denmark (Borgervænget 3, 2100 Copenhagen, Denmark), j.no. R-20075058. Retrospective studies do not require informed consent in Denmark.

2.1 | Hypotheses

We hypothesize that larger areas above the MAP-curve but below a threshold for hypotension, the hypotensive area, during cardiopulmonary bypass are associated with increased risk of gastrointestinal complications after cardiac surgery.

2.2 | Study Population

All patients who underwent cardiac surgery in the Department of Cardiothoracic Surgery, Copenhagen University Hospital—Rigshospitalet between January 1st, 2018 to December 31st, 2022 will be assessed for eligibility. The study period corresponds to the data availability in the database.

2.2.1 | Inclusion Criteria

- Age ≥ 18 years and registered in the Danish Civil Registration System
- Any of: cardiac valve surgery, coronary artery bypass grafting, and ascending aorta reconstruction
- Cardiopulmonary bypass

2.2.2 | Exclusion Criteria

- More than 10 consecutive minutes with unrealistic mean arterial blood pressure readings during cardiopulmonary bypass, i.e., less than 15 mmHg or above 120 mmHg

The purpose of the exclusion criterion is to reduce the impact of longer consecutive durations of artifacts from manipulation, flushing, and/or misplacement of the arterial line.

2.3 | Exposure

2.3.1 | Definition

The exposure will be a continuous measure, hypotensive area, quantifying the absolute burden of hypotension during cardiopulmonary bypass. The hypotensive area will be defined as the area above the MAP-curve and below a threshold for hypotension (Figure 1). The threshold for the primary analysis will be universal, however for the sub-group analysis, subgroup-specific thresholds will be applied in addition to the universal threshold. Without placing a such threshold, the area under the MAP curve would simply equal the mean MAP multiplied by the duration of the surgery. The mathematical definition of the hypotensive area is explained in detail in the Supplemental Appendix ("Hypotensive area"—Calculating hypotensive area, and Figures S.1 and S.2). The threshold will be determined according to a data-driven algorithm.

2.3.2 | Threshold Selection

Hypotensive area differs depending on the threshold-level which is chosen. To determine the optimal threshold-level, a data-driven decision-algorithm will therefore be applied, drawing on principles from machine-learning methodology also commonly used in cardiac surgery risk prediction [11].

The data will be separated into training data (75%) and validation data (25%), such that threshold selection (training) is performed independently of endpoint assessment (validation) to avoid overfitting and induction of bias. The training data to validation data ratio was chosen to retain most observations for stable estimation of the threshold while reserving a sufficiently large independent sample for validation. The training data will further be equally divided into three subsamples which will be recombined for cross-validation training to increase the likelihood of a stable optimal threshold estimate (Figure 2).

The divisions of the data will be stratified to balance interactions and between-sample risk of gastrointestinal

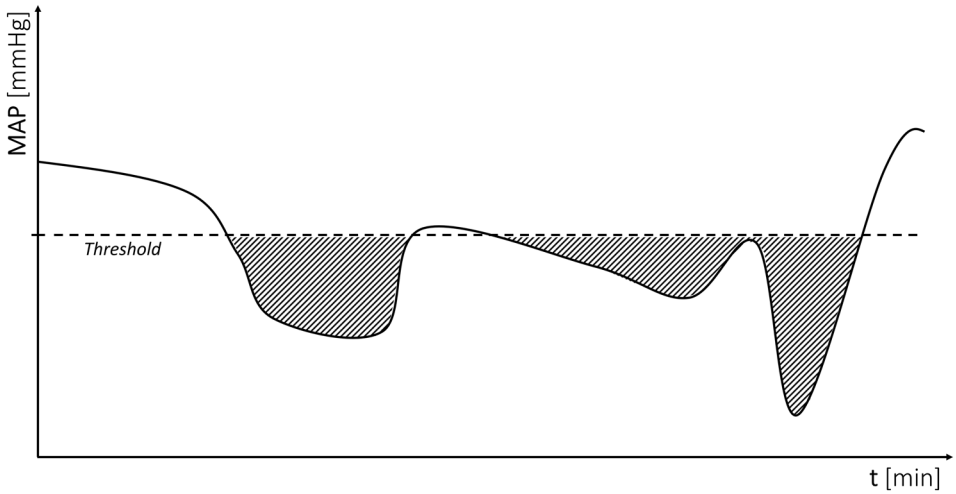


FIGURE 1 | The area between the mean arterial blood pressure (MAP) curve and the threshold (while below the threshold) will be calculated for each patient and used as the exposure. The threshold will be defined from an algorithm.

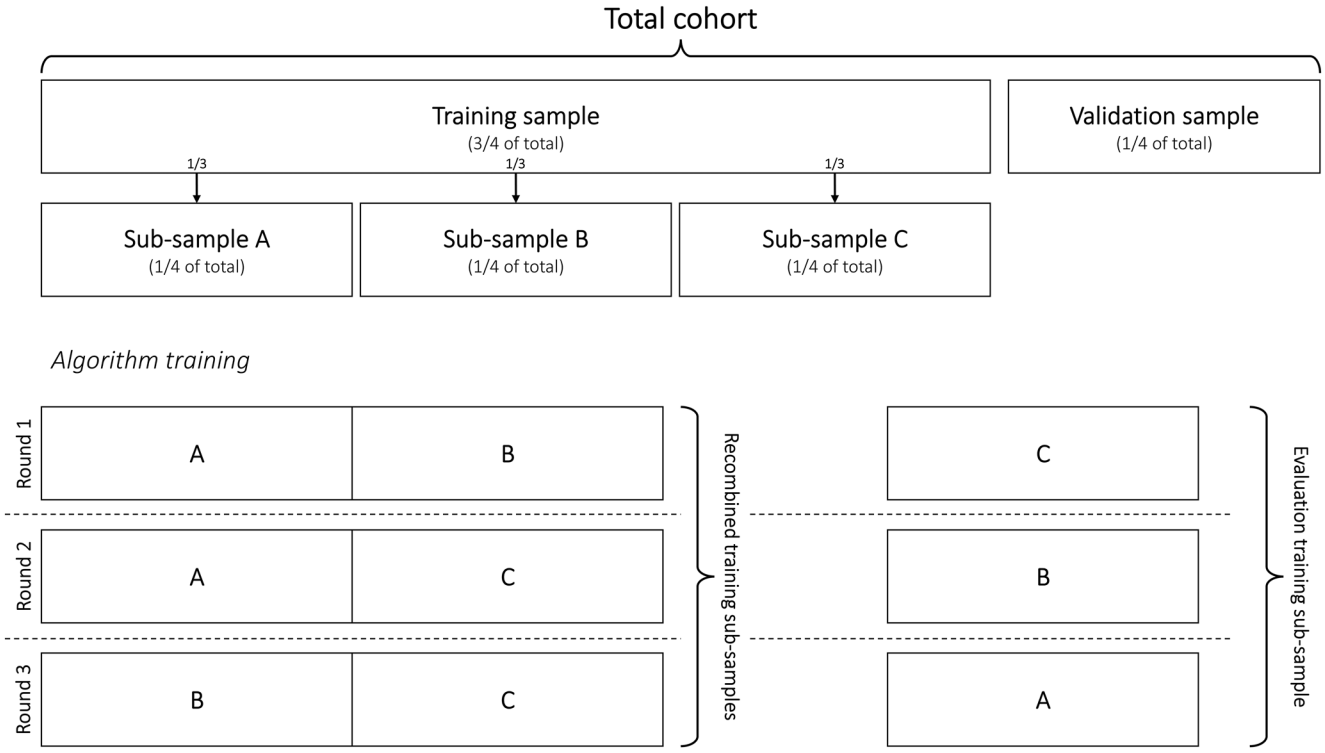


FIGURE 2 | Division of the cohort into training samples and a validation sample. Training samples will be subdivided and recombined to increase training sub-sample size and reduce the risk of random error and overfitting affecting threshold selection. The remaining training sub-sample will be used as an evaluation sample for each training round.

complications. These variables will be the suspected confounders and potential effect modifying variables with expected data availability for all subjects, being age, body mass index, chronic obstructive pulmonary disease, diabetes mellitus, type of surgery, urgency of surgery, pre-procedural mean arterial blood pressure, cardiopulmonary bypass duration, aortic cross-clamp duration, number of minutes with pump-flow $\geq 2.5\,L/min/m^2$, renin-angiotensin-aldosterone inhibitor administered prior to surgery, calcium-channel antagonist administered prior to surgery, norepinephrine-equivalents mean rate during cardiopulmonary bypass, and extracardiac arteriopathy. This corresponds to all the variables outlined in the "Subgroup analysis" section and under "Confounding" in the "Statistics" section—with the exception of computed tomography derived measurements as these are not expected to be available for all or most subjects.

For each recombined training sample, receiver operator characteristics (ROC) and the area under the ROC-curve (AUC_{ROC}) will be calculated on the primary endpoint for all thresholds within the 2.5 to 97.5 percentile of MAP values with increments of 1 mmHg.

The threshold-level with best discriminatory power based on the largest AUC_{ROC} from the recombined training sample will then be evaluated on the remaining training sub-sample, yielding another AUC_{ROC} (Figure S.3).

This will be repeated in three rounds for each of the three combinations of training sub-samples. The threshold-level yielding the highest AUC_{ROC} obtained from threshold testing on evaluation training sub-samples will be decided as the final threshold-level for the validation sample (Figure S.4). However, if the evaluation training sub-sample has a higher AUC_{ROC} than the recombined training subsample, the AUC_{ROC} of the recombined training subsample will be used for threshold decision to avoid overfitting.

Sensitivity, specificity, positive predictive value, negative predictive value, and "number needed to treat" for the selected threshold will be reported.

2.3.3 | Grouping

The study population will be divided based on hypotensive area above or below a cut-off.

This cut-off will be the point on the ROC-curve of the complete training sample at the algorithm-selected threshold that maximizes sensitivity while also misclassifying all event-free subjects as cases. A constrained approach is not feasible as we do not know if we will achieve sensitivities above for example, 80% with meaningful specificities. Therefore, a weighted Youden index will be applied:

$$J_w = w \times \text{Sensitivity} + (1-w) \times \text{Specificty}, \quad w = 0.80 \qquad (1)$$

The cut-off will be the threshold maximizing the weighted Youden index, weighing sensitivity 80% and specificity 20%.

Endpoints will also be explored with hypotensive area as a continuous exposure using restricted cubic splines.

2.4 | Endpoints

Endpoints will be derived from electronic registrations in Epic combined with specific thresholds for manual validation as defined in the Supplemental Appendix. For composite outcomes, the components will also be reported individually.

2.4.1 | Primary Endpoint

The primary endpoint will be major gastrointestinal complications within 30 days, a composite of acute intestinal ischemia, abdominal surgery, bowel perforation, and gastrointestinal hemorrhage.

Acute intestinal ischemia, bowel perforation, and gastrointestinal hemorrhage will be defined by patient records with evidence of a clinician or radiologist having diagnosed the patient as such (Table S.1). Abdominal surgery will be defined as registration with any procedural code corresponding to bowel resection, diagnostic abdominal surgery (Table S.2), or patient records with evidence of abdominal surgery.

2.4.2 | Secondary Endpoints

1. Serious gastrointestinal complications within 30 days, a composite of acute intestinal ischemia, bowel perforation, gastrointestinal hemorrhage, ileus, clostridium difficile colitis*, abdominal intervention**, and hepato-biliary-pancreatic dysfunction***.
2. Delayed recovery of bowel function (any of: ≥ 8 units macrogol within the same date, any rectally administered laxative, any opioid antagonist laxative, or any type of laxative for ≥ 5 consecutive days that was not used prior to surgery, Table S.8).
3. Cholinesterase inhibitor administration (e.g., neostigmine) within 30 days (combined anticholinergics and cholinesterase inhibitors will not be considered events).
4. Death within 30 days.

*Ileus and clostridium difficile colitis will be defined by patient records with evidence of a clinician or radiologist having diagnosed the patient as such (Table S.3).

**Abdominal intervention will be defined as abdominal surgery (corresponding to primary endpoint definition) or a registration with any procedural code corresponding to endoscopy (Table S.7).

***Hepato-biliary-pancreatic injury will be defined as any of: (1) clinical diagnosis of hepatic failure, cholangitis, cholecystitis or pancreatitis in patient records, (2) meeting American College of Gastroenterology 2023 criteria for acute hepatic failure (with

exception of altered mental status) [12], (3) meeting the 2011 drug-induced liver injury (DILI) Expert Working Group criteria for hepatobiliary injury [13], or (4) elevated pancreatic enzymes corresponding to the 2025 International Association of Pancreatology Revised Guidelines on Acute Pancreatitis [14] (Tables S.4–S.6).

2.4.3 | Explorative Endpoints

1. Acute kidney injury (within 7 days, according to the Kidney Disease: Improving Global Outcomes 2012 guidelines on acute kidney injury [15], Table S.9).
2. Peak arterial lactate postoperatively within 30 days.
3. Peak bilirubin (total) postoperatively within 30 days.

2.5 | Data Sources

Data from various sources (Epic, Patient Analysis and Tracking System—PATS, and pump-flow data) has been collected, cross-validated and stored in a database which will be the primary source for this study. Baseline characteristics to be collected are outlined in Table 1.

2.6 | Subgroup Analysis

Subgroup analysis will be performed on the primary endpoint on the below variables:

1. Surgery type.
2. Urgency of surgery (anesthetised within 12 h from scheduling, yes vs. no).
3. Age (≥ 65 years vs. < 65 years).
4. Cardiopulmonary bypass duration.
5. Aortic cross-clamp duration.
6. Number of minutes with pump-flow ≥ 2.5 L/min/m^2.
7. Renin-angiotensin-aldosterone inhibitor administered prior to surgery (Table S.10).
8. Calcium-channel antagonist administered prior to surgery (Table S.11).
9. Norepinephrine-equivalents mean rate during cardiopulmonary bypass (Table S.12).
10. Extracardiac arteriopathy (Table S.13).
11. Abdominal aortic calcium-score (Figure S.5).
12. Total enteric cross-sectional artery-area (TECSA).
13. Pre-procedural MAP.

The analysis will be performed on all strata of categorical subgroups, and above vs. below median for continuous subgroup variables unless specified otherwise. For exact definitions of non-self-explanatory subgroups, refer to the Supplemental Appendix ("Subgroup definitions").

The analysis will be run twice for each subgroup—once with the global hypotension threshold, and then once again with a subgroup-specific threshold.

2.7 | Statistics

Statistics will be performed in R (version 4.6.0 or newer) from R Foundation for Statistical Computing, Vienna, Austria.

2.7.1 | Endpoint Analysis

The dichotomous endpoints will be assessed by logistic regression. Continuous endpoints will be assessed using single and multiple linear regression. Hypotensive area will be modeled as a binary exposure, as well as a continuous exposure using restricted cubic splines.

TABLE 1 | Patient characteristics planned to be obtained.

Preoperative		Surgery
Age	COPD	Urgency[b]
Sex	Diabetes Mellitus	EuroSCORE II
Body mass index	Extracardiac arteriopathy[a]	Procedures
Smoking status	Creatinine	Surgery duration
LVEF	Estimated glomerular filtration rate	Duration of cardiopulmonary bypass
Atrial fibrillation or flutter	Hematocrit	Cross-clamp time
MAP		Pump flow

Note: Comorbidities will be defined from ICD-10 diagnosis codes at the time of admission. Additionally, collecting a prescription of metformin within 180 days prior to surgery will be considered equivalent of diabetes mellitus.
Abbreviations: COPD, chronic obstructive pulmonary disease; EuroSCORE II, European System for Cardiac Operative Risk Evaluation (2nd version); LVEF, left ventricular ejection-fraction; MAP, mean arterial blood pressure.
[a]Defined as carotid artery stenosis or occlusion, intermittent claudication, chronic mesenteric ischemia, and prior ischemic stroke or transient ischemic attack.
[b]Emergency surgery will be defined as surgery within 12 h from case-booking. The remainder will be classified as non-emergency surgery, covering elective and urgent cases.

2.7.2 | Confounding

Multivariate regressions will be adjusted for known and suspected confounders. These are:

1. Age.
2. Diabetes mellitus.
3. Chronic obstructive pulmonary disease.
4. Cumulative intraoperative remifentanil dose.
5. Urgency (anesthetised within 12 h from scheduling).

2.7.3 | Missing Data

Mean arterial blood pressures outside the range of 15 to 120 mmHg will be considered invalid and will be treated as missing. Missing blood pressure data will be imputed using forward-fill and backward-fill, choosing forward over backward fill when the distance to the nearest trusted value is equal. Missing data on outcomes is not expected.

2.7.4 | Regression Model Diagnostics

Linearity of continuous covariates on the log-odds will be assessed. If a continuous covariate is not considered linear, it will be included in the regression as a categorical variable instead. Linearity of covariates and distribution of continuous endpoints will be assessed by scatterplots including the fit.

The continuous endpoints (peak bilirubin and peak arterial lactate) may be log-transformed if severely skewed. Histograms and standardized residuals plotted against the fitted values will be assessed for normality and homoscedasticity. Non-linear covariates will be categorized.

All decisions to adapt analyses will be made based on training data diagnostics only.

2.7.5 | Exposure Analysis

As the hypotensive area is a two-dimensional variable including time, variance may be inflated by the duration of cardiopulmonary bypass. A such semi-structural multicollinearity is however not a statistical issue when interpreting regression coefficients if both variables are not independently included in the model.

Yet, significant correlation between the hypotensive area and the duration of cardiopulmonary bypass is important to investigate, as this will affect the interpretation of the results, especially in the case of a high threshold level. This could otherwise lead to the potential misconception that MAP below a (high) threshold is associated with a worse outcome in a scenario where the duration of cardiopulmonary bypass has a strong independent association with gastrointestinal complications.

The data distribution of MAP during cardiopulmonary bypass will be assessed and compared to the threshold. This should indicate if the threshold is clearly driven by time more than by MAP deficit.

Plots of the hypotensive area as a function of time above threshold, cardiopulmonary bypass duration, and median MAP, respectively, will be created for visual inspection. Also, plots of time below threshold as a function of time above threshold, total cardiopulmonary bypass duration, and aortic cross-clamp time will be made. Linear correlations (or linearly transformed correlations if necessary) will be assessed by slope (β) and Pearson's correlation (ρ).

2.7.6 | Sample Size Considerations

Detecting an odds ratio OR = 3.0 at a significance-level $\alpha = 5\%$, power 1-$\beta = 80\%$, assuming a 1:1 allocation, and an event-rate of 1.0% among unexposed, this requires a total of 1816 surgeries to be included, based on the z-test with continuity correction.

Assuming 1500 surgeries per year and a study period of 5 years, this yields a total of 7500 patients. As the validation sample will consist of 1/4 of the total sample (expected $N = 1875$), the study should be sufficiently powered for detecting an OR of ≤ 3.0.

2.7.7 | Data Distribution

The distribution of continuous variables will be assessed visually by histograms and Q–Q plots.

2.7.8 | Statistical Tests

For logistic regressions, the Wald test is used. For linear regressions, one-sample *t*-test will be used for continuous predictors and two-sample *t*-test for binary predictors. A p-value < 0.05 will be considered significant to reject the null hypothesis.

2.7.9 | Presentation

Continuous variables will be presented either as means with 95% confidence intervals or medians with interquartile ranges depending on the distribution of the data. Categorical variables will be presented as proportions.

Dichotomous endpoints will be presented as OR and 95% CI. Primary and secondary endpoints will be visualized by cumulative incidence plots (or Kaplan–Meier curves) stratified by group, and by plotting the hypotensive area continuously against the OR. The subgroup analysis will be visualized in a forest plot.

3 | Discussion

This retrospective study will assess if the hypotensive area during cardiopulmonary bypass in cardiac surgery is associated with gastrointestinal complications.

The strengths of this study include a data-driven approach to define a threshold discriminating high versus low blood pressure during cardiopulmonary bypass in cardiac surgery on the risk of gastrointestinal complications. Using continuous measurements of invasive mean arterial blood pressure with intervals of 1 min we will catch the magnitude and duration of temporary dips in blood pressure that would not be captured by means, medians or single-point measures.

However, there are some limitations. As gastrointestinal complications are relatively rare, the power to detect differences between groups is low. Mitigating this by using a composite outcome comprising both lethal and relatively benign complications may reduce clinical relevance. Causality cannot be inferred from retrospective data, and the study may be prone to confounding by indication.

In conclusion, the results from this study may lead to relevant hypotheses for prospective testing.

Author Contributions

Valdemar Rømer: conceptualization; methodology; data curation; visualization; writing – original draft, review and editing. **Sebastian Wiberg:** methodology; data curation; writing – review and editing. **Theis Skovsgaard Itenov:** methodology; data curation; writing – review and editing. **Jesper James Linde:** methodology; writing – review and editing. **Matthias Corbascio:** conceptualization; methodology; writing – review and editing; supervision. **Bo Laksáfoss Holbek:** conceptualization; methodology; writing – review and editing; supervision.

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The authors have nothing to report.

Conflicts of Interest

Bo Laksáfoss Holbek reports consultancy agreement with Medtronic and speaker's fee from Medela. The remaining authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S.1:** Illustration of the hypotensive area (dashed) and the variables associated with it. **Figure S.2:** By creating a modified mean arterial blood pressure (mMAP), the hypotensive area (dashed) is the difference between the Thresholdtime area (Panel A, blue area) and the mMap-time area (Panel B, orange area). **Figure S.3:** Thresholds for hypotension will be set from recombined training-samples and evaluated on the remaining training sub-sample. This will be done for each combination of recombined sub-samples and evaluation sub-samples. **Figure S.4:** The largest area under receiver-operator-curve for the evaluation training sub-samples dictate the final threshold for hypotension. **Figure S.5:** Segmentation of the abdominal aorta for use in this study. Generated with ChatGPT, modified in Microsoft Powerpoint. **Table S.1:** Major gastrointestinal complications with corresponding ICD-10 diagnosis codes that will trigger manual confirmation and registration of time of onset from patient records. **Table S.2:** Abdominal surgery procedural codes. **Table S.3:** Gastrointestinal complications with corresponding ICD-10

diagnosis codes that will trigger manual confirmation and registration of time of onset from patient records. **Table S.4:** The three criteria used in this study for definition of hepatic injury following cardiac surgery. **Table S.5:** If any of the above criteria are met, the patient will be classified as having hepatobiliary dysfunction. **Table S.6:** Pancreatic injury. **Table S.7:** Abdominal interventions with corresponding SKS codes. **Table S.8:** Delayed bowel recovery. If any criterion is met, the patient will be considered as having had delayed recovery of bowel function. **Table S.9:** For the acute kidney injury endpoint to be triggered, any of the above criteria must be true. **Table S.10:** Renin-angiotensin-aldosterone system inhibitors. **Table S.11:** Calcium-channel antagonists. **Table S.12:** Equivalent doses of vasoactive drugs as compared to norepinephrine. **Table S.13:** Extracardiac arteriopathy will be defined as any of the ICD-10 codes being registered prior to surgery.