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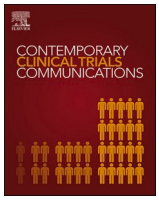

The hypotension prediction index in major abdominal surgery – A prospective randomised clinical trial protocol

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ABSTRACT

Background: Patients undergoing major abdominal surgery are at increased risk of developing perioperative hypotension, which is associated with increased mortality and morbidity. Despite using advanced technologies such as evaluating arterial pressure derived cardiac output, anaesthetic management to maintain hemodynamic stability is still reactive when the clinical decision is made after hypotension has developed. Previous perioperative goal-directed studies have not proven the benefits of this approach with high certainty. A new, approved technology called the Hypotension Prediction Index (HPI) aims to prevent hypotension occurrence by allowing the precise hemodynamic monitoring of patients under general anaesthesia, significantly reducing intraoperative hypotension events. This prospective randomised clinical trial aims to compare the rate of perioperative hypotension in patients undergoing major abdominal surgery according to their type of hemodynamic monitoring.

Methods: and Analysis: Patients meeting the inclusion criteria will be randomly assigned to receive hemodynamic assessment with arterial pressure cardiac output (APCO) monitoring (group A) or hemodynamic monitoring with the HPI software (group B). The primary outcome is a time-weighted average (TWA) mean arterial pressure (MAP) of <65 mmHg: TWA MAP = (depth of hypotension [in mmHg] below a MAP of 65 mmHg × time [in minutes] spent below a MAP of 65 mmHg)/total duration of the operation (in minutes). Its secondary outcomes include perioperative hemodynamic management and the rate of postoperative complications.

Ethics and dissemination: This trial was approved by the Ethics Committee of the Poznan University of Medical Sciences (KB–559/220; date: 01/07/2022). Its results will be submitted for publication in a peer-reviewed journal.

Trial registration number: NCT06247384.

1. Background

The fundamental aspect of perioperative anaesthetic management is maintaining hemodynamic stability, focusing on avoiding or reducing intraoperative hypotension (IH) episodes. Due to wide variability in the definitions of perioperative hypotension, it is challenging to establish guidelines for optimal hemodynamic management in different surgical scenarios [1]. However, many studies have shown increased mortality and morbidity due to low perioperative blood pressure [2–14]. Among the factors influencing the rate of perioperative complications, the type of surgery is important, with major abdominal surgery having the highest rate of perioperative complications [15]. One study performed on 308 patients undergoing major abdominal surgery showed that hypotension requiring an infusion of noradrenaline was a risk factor for major complications within 30 days postoperative [16]. On the other hand many data on the postoperative complications come from observational studies. A metanalysis published in 2023 showed some surprising results regarding the targeted perioperative MAP and postoperative outcomes [17]. The authors analysed 10 randomised controlled trials with more than 9000 patients which compared permissive management with MAP <60 mmHg and targeted management with MAP> 60 mmHg. Surprisingly, there were no differences in mortality among analysed groups, but patients who had MAP <60 mmHg had less episodes of atrial fibrillation and had shorter hospital stay [17].

Monitoring the cardiovascular system using advanced techniques such as measuring the arterial pressure-based cardiac output (APCO) and implementing the derived parameters into treatment algorithms, so-

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called goal-directed therapy (GDT), seems essential for performing good-quality anaesthesia. Despite many studies assessing GDT within various types of surgery, recently published meta-analyses showed no reduction in perioperative morbidity and mortality [18,19].

One possible reason for the failure of studies using advanced hemodynamic monitoring is the reactive approach implemented in GDT protocols. Mean arterial pressure (MAP), stroke volume, stroke volume variation (SVV), or pulse rate could not predict IH events in patients undergoing major surgery [20].

A recently developed technology called the Hypotension Prediction Index (HPI) aims to detect episodes of hypotension with a MAP of <65 mmHg before they occur. HPI is a unitless number between 0 and 100, with higher numbers indicating a greater risk of hypotension. The HPI algorithm analyses the arterial pressure curve and, with a specificity and sensitivity of around 90 %, can predict hypotension episodes up to 10 min before they occur [21].

Despite an increasing number of clinical studies demonstrating the beneficial effects of the HPI on reducing perioperative hypotension, there remain some issues that must be overcome. Only scarce data exists on the reduced perioperative complications related to HPI use [22,23]. One fundamental question is whether the HPI will reduce hypotension episodes better than advanced hemodynamic monitoring of the APCO.

2. Study aim

This prospective randomised clinical trial aims to compare the rate of hypotension in patients undergoing major abdominal surgery with different types of hemodynamic monitoring. Based on the retrospective data, the hypothesis is that the HPI algorithm will reduce the time-weighted average (TWA) of IH below a MAP threshold of 65 mmHg compared to the APCO algorithm.

3. Methods

3.1. Study design

This prospective randomised clinical trial will be performed at the Poznan University of Medical Science Hospital. Patients meeting the eligibility criteria (see Section 3.6) will be randomly assigned to receive hemodynamic monitoring with the APCO algorithm (FloTrac sensor; Edwards Lifesciences, Irvine, CA, USA) (Group A) or the HPI algorithm (Acumen IQ sensor, Edwards Lifesciences, Irvine, CA, USA) (Group B).

This trial has been approved by the Ethics Committee of Poznan University of Medical Science (KB–559/220; date: 01/07/2022) and registered at ClinicalTrials.gov (NCT06247384).

3.2. Randomisation

Envelope randomisation will be performed using blocks of 10.

3.3. Blinding

The participants will not be aware of their group allocation. While intraoperative personnel will not be blinded to the monitoring allocation, the data analysis will remain blinded.

3.4. Duration

Duration per patient: The participants will be randomised the day before their surgical procedure. Their basic demographic, morphometric, clinical, and laboratory data will be collected the day before surgery. Their hemodynamic monitoring will start before anaesthesia induction and end with anaesthesia cessation in the operating room. Postoperative screening will take place on the first postoperative day. The participants will be followed up on day 30 after randomisation. Trial duration: The planned start date is 1 November 2024, and the planned end date is 31 December 2025.

3.5. Study groups

Patients meeting the eligibility criteria for this trial (see Section 3.6) will be randomly assigned to one of the two study groups. Those in Group A will receive hemodynamic monitoring with the APCO algorithm (FloTrac sensor), and those in Group B will receive hemodynamic monitoring with the HPI algorithm (Acumen IQ sensor).

3.6. Patient enrolment

3.6.1. Inclusion criteria

- Patients qualified for elective major abdominal surgery, defined as an expected duration of more than 2 h, an estimated blood loss of >15 % of blood volume, or an expected transfusion requirement of at least two packed red blood cells with general or combined anaesthesia.
- Patients with American Society of Anesthesiologists (ASA) status III or IV.
- Written informed consent.

3.6.2. Exclusion criteria

- Patients aged under 18 years.
- Lack of health insurance.
- Pregnancy.
- Known history of
- congenital heart disease,
- severe aortic and/or mitral stenosis or
- heart failure and an ejection fraction of <35 %.
- Persistent atrial fibrillation and other arrhythmias impairing APCO/HPI monitoring

3.7. Patient and public involvement

Patients or the public were not involved in the trial's design, conduct, reporting, or dissemination plans.

4. Study protocol

4.1. Interventions

All patients will receive general anaesthesia using typical drug regimens according to the local protocol. In addition to standard monitoring, all patients will have an arterial line inserted into the radial artery before anaesthesia induction.

4.1.1. Group A – APCO monitoring

Patients in Group A will receive hemodynamic monitoring using the APCO algorithm with a FloTrac sensor. The therapeutic decision regarding treating hypotension using fluids, vasopressors or inotropic agents will be based on the Goal-Directed Therapy Protocol (Fig. 1).

4.1.2. Group B – HPI monitoring

Patients in Group B (HPI) will receive hemodynamic monitoring using the HPI algorithm with an Acumen IQ sensor connected to the HemoSphere platform. Their hemodynamic management will be based on the HPI indications and algorithm shown in Fig. 2, which considers hypovolemia, impaired contractility and vasoplegia. An alert appears on the monitor screen when the HPI value exceeds 85, and then the clinician must make a therapeutic decision to avoid a hypotensive episode.

The trial-related hemodynamic management will end when the surgery ends. The participants will be referred to the postoperative or intensive care unit according to their clinical indications.

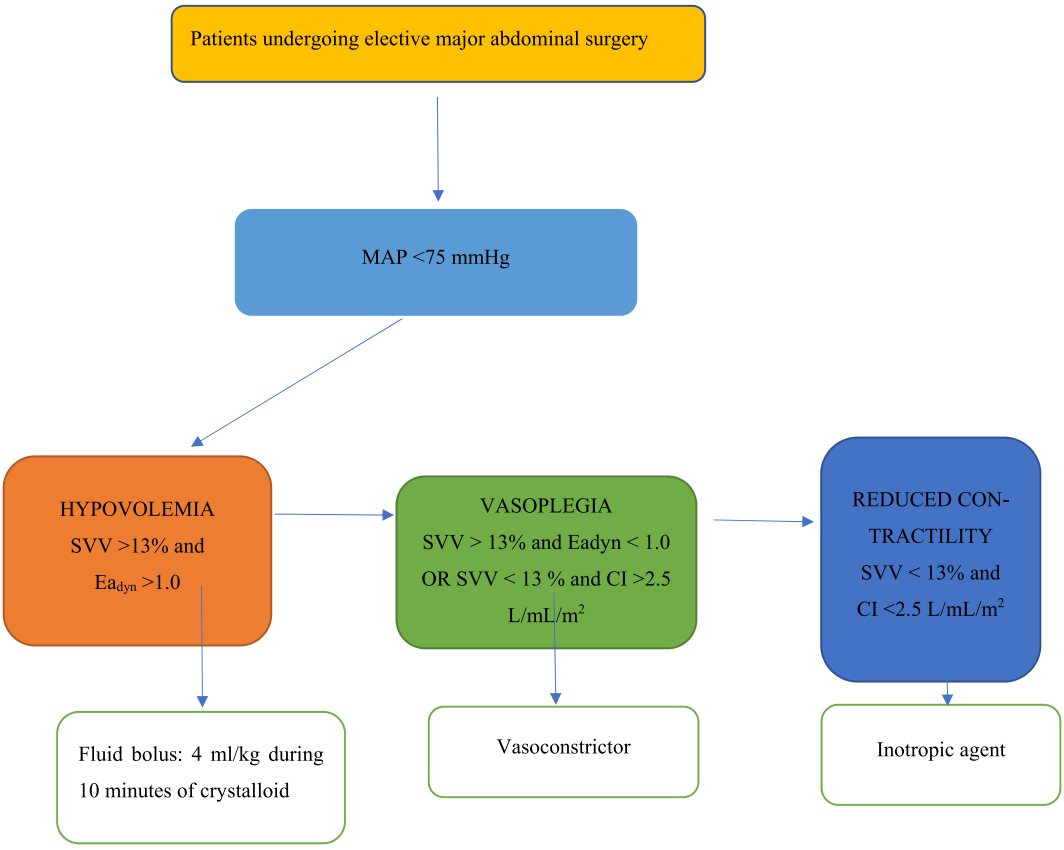

Fig. 1. The Goal-Directed Therapy Protocol for Group A (APCO). Abbreviations: CI, cardiac index; Ea_{dyn}, dynamic arterial elastance; MAP, mean arterial pressure; SVV, stroke volume variation.

4.2. Measurements

4.2.1. Preoperative data

Baseline information: demographic and morphometric data, including age, weight, height, sex, and ASA physical status, will be analysed. History of cardiovascular disease, pulmonary disease, diabetes, chronic liver disease, chronic kidney failure, neurologic disease and preoperative drug administration will be collected. Preoperative results of electrocardiograms (ECGs) and laboratory tests, including morphology, coagulation parameters, and blood levels of glucose, electrolytes, blood urea nitrogen, creatinine, troponins and N-terminal prohormone of brain natriuretic peptide (NT-proBNP), will be recorded.

4.2.2. Perioperative data

Intraoperative anaesthesia data will include the volatile anaesthesia dose, calculated as minimum alveolar concentration hours, and the total doses of opioids, propofol, ketamine and other hypnotics. Bispectral index (BIS), temperature measured at the oesophagus, diuresis, and pulmonary and hemodynamic standard parameters, including heart rate (HR) and invasive blood pressure, will be recorded at regular intervals. The total doses of vasopressors and fluids, including crystalloids, colloids and blood products, will be recorded.

Hemodynamic monitoring data from the FloTrac sensor (Group A) and Acumen IQ sensor via the HemoSphere platform (Group B) will be recorded intraoperatively, including HR; systolic, diastolic, and mean blood pressure; cardiac output; cardiac index (CI); stroke volume; stroke volume index; stroke volume variation (SVV); pulse pressure variation (PPV); systemic vascular resistance; systemic vascular resistance index (SVRI); and dynamic arterial elastance (Ea_{dyn}).

4.2.3. Follow up.

The participants will be screened for specific organ injury during the postoperative period. On the first, second and fifth postoperative day, troponin, NT-proBNP and creatinine levels will be assessed. Other secondary outcomes, including hospital stay length, will be evaluated.

4.3. Outcome measures

The TWA of MAP was calculated as (depth of hypotension [in mmHg] below the specified MAP threshold × time [in minutes] spent below the specified MAP threshold)/total duration of the operation (in minutes), with the threshold varying between the primary and secondary endpoints.

4.3.1. Primary endpoint

1. TWA for a MAP of <65 mmHg.

4.3.2. Secondary endpoints

1. TWA for a MAP of <50 mmHg.
2. TWA for a MAP of >90 mmHg.
3. TWA for a MAP of >100 mmHg.
4. Thirty-day mortality.
5. Hospitalisation length.
6. Myocardial injury, evaluated based on postoperative serum troponin levels (defined as hsTnT >65 ng/L).
7. Kidney injury, evaluated based on postoperative serum creatinine levels (increase in sCr by ≥ 0.3 mg/dL within 48 h; increase in sCr to 1.5 times baseline; or urine volume less than 0.5 mL/kg/h for 6 h).
8. Intraoperative fluid administration.
9. Intraoperative vasopressor dose.

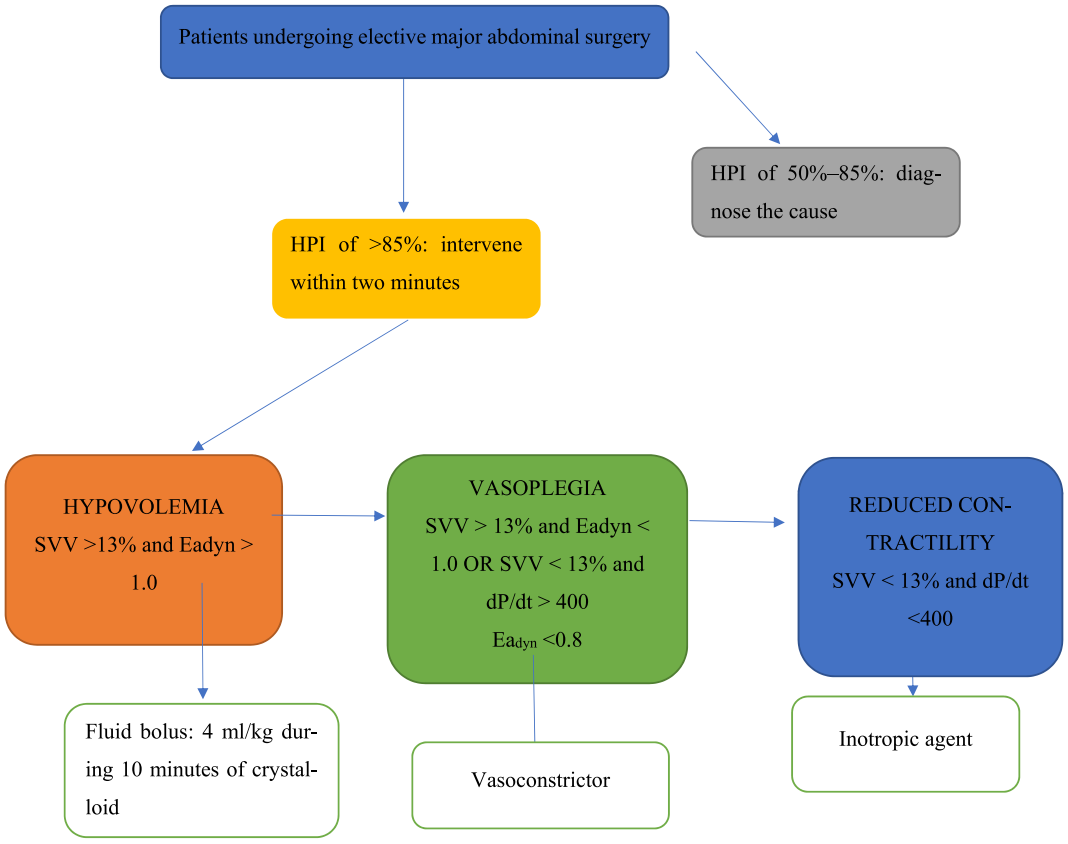

Fig. 2. HPI management algorithm for Group B. Abbreviations: dP/dt, the rate of pressure change with time during isovolumic contraction of the cardiac ventricles; Ea_{dyn}, dynamic arterial elastance; SVV, stroke volume variation.

10. Rate of intra and postoperative atrial fibrillation

5. Statistical analysis

5.1. Sample size calculation

An analysis of data from patients who underwent major abdominal surgery with advanced hemodynamic monitoring showed a mean TWA for a MAP of <65 mmHg of 1.18 ± 2.51 mmHg with FloTrac monitoring and 0.20 ± 0.32 mmHg with HPI monitoring. Based on these values, the estimated sample size was 103 patients per group, considering 80 % power and a type one error of 5 % ($p < 0.05$) calculated using an online platform [24]. The number of patients in both groups will be increased by 10 % due to considered drop out rate.

5.2. Study populations

Adult patients undergoing major abdominal surgery who meet the eligibility criteria.

5.3. Study groups

Group A: APCO hemodynamic monitoring.
Group B: HPI hemodynamic monitoring.

5.4. Statistical analysis

The normality of the data distribution will be assessed using the D'Agostino–Pearson test. Continuous variables will be expressed as the mean ± standard deviation when normally distributed or the median (interquartile range) when non-normally distributed. Categorical variables will be expressed as the frequency (percentage). Quantitative variables will be compared between Groups A and B using the independent samples *t*-test (normally distributed) or Mann–Whitney *U* test (non-normally distributed). Categorical variables will be compared between Groups A and B using the chi-squared test. A $p < 0.05$ will be considered statistically significant. All statistical analyses will be performed using the MedCalc® statistical software (version 20.115; MedCalc Software Ltd., Ostend, Belgium).

6. Study phases

6.1. Enrolment

The researchers will screen all patients scheduled for elective major abdominal surgery against the inclusion and exclusion criteria. Informed consent will be obtained from participants the day before surgery. Their demographics and comorbidities will be collected before randomisation into Groups A (APCO) and B (HPI), which will be performed the day before surgery with an envelope block size of ten. The participants will not be aware of their group allocation. While the anaesthesiologic personnel will not be blinded to participants' group allocation, the data analysis will remain blinded. All researchers will receive training in managing hemodynamic monitoring and compliance with the hemodynamic protocols. A Consolidated Standards of Reporting Trials (CONSORT) flowchart of this trial is shown in Fig. 3.

6.2. Treatment phase

Participants in both groups will undergo general anaesthesia with basic monitoring constituting five-lead ECG, pulse oximetry, BIS monitoring (Medtronic, Dublin, Ireland), a peripheral and central intravenous line and an indwelling radial arterial catheter.

All participants will receive general or combined general and

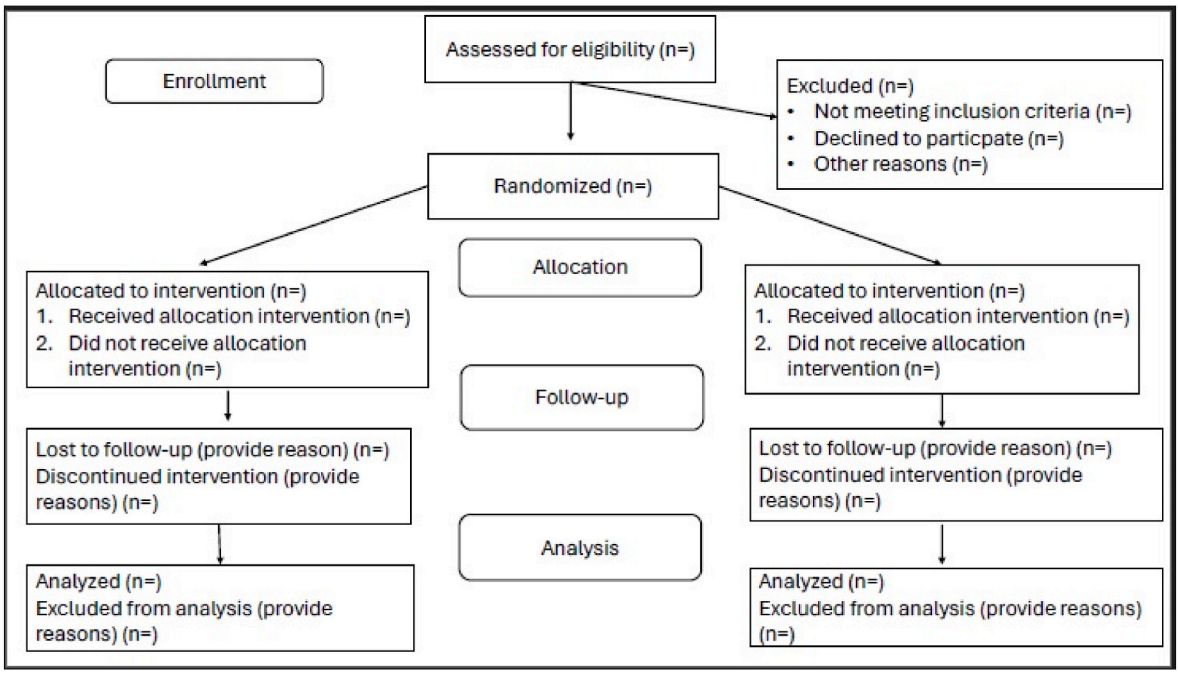

Fig. 3. CONSORT flowchart of the trial.

epidural anaesthesia at the attending anaesthesiologist's discretion. The administration of the drugs used to induce anaesthesia and neuromuscular agents will be at the anaesthesiologist's discretion. Anaesthesia will be maintained with sevoflurane with a BIS of 40–60. All participants will receive invasive and continuous arterial pressure monitoring with a FloTrac sensor (Group A) or an Acumen IQ sensor (Group B). The hemodynamic optimisation algorithms will begin immediately after placing the arterial catheter and inducing anaesthesia. Participants in both groups will receive maintenance fluid infusion of balance crystalloids with a rate of 5–7 mL/kg/h, and packed red blood cells will be transfused if their haemoglobin levels fall below 8 g/dL.

In Group A, hemodynamic management will aim to maintain a MAP of >65 mmHg and be based on data provided by APCO monitoring using the FloTrac sensor. The APCO algorithm is shown in Fig. 1. If the SVV exceeds 13 % and a calculated Eadyn will be > 1 a fluid bolus of 4 ml/kg during 10 min will be administered. A infusion of noradrenaline with a rate of 0.01–0.4 mcg/kg/min will be administered when the SVV >13 % and calculated, Ea_{dyn} is < 1.0, or when SVV is <13 % and CI > 2.5 L/mL/m^2, An infusion of Dobutamine with a rate of 1–15 mcg/kg/min will be administered when the CI falls below 2.5 L/mL/m^2 and SVV is <13 %

In Group B, hemodynamic monitoring will be based on the hemodynamic parameters derived from the Acumen IQ sensor and HPI platform, including some that are unavailable with the APCO platform: the rate of pressure change with time during isovolumic contraction of the cardiac ventricles (dP/dt), Ea_{dyn} and HPI. The HPI algorithm is shown in Fig. 2, with the interventions based on the three main mechanisms leading to hypotension: hypovolemia, impaired contractility and vasoplegia. The secondary screen parameters will be examined when the HPI goes above 85. A fluid bolus of 4 ml/kg of a crystaolloid during 10 min will be administered if the SVV exceeds 13 % and the Ea_{dyn} exceeds 1. A infusion of noradrenaline with a rate of 0.01–0.4 mcg/kg/min will be administered when the SVV >13 % and calculated Ea_{dyn} is < 1.0, or when SVV is <13 % and dP/dt > 400. An infusion of dobutamine with a rate of 1–15 mcg/kg/min will be administered when the dP/dt falls below 400 and SVV is <13%indicating impaired contractility.

The HemoSphere platform will record the hemodynamic data every 20 s, which will be downloaded after the end of anaesthesia for offline analysis.

6.3. *Daily assessment*

Standard laboratory parameters will be obtained during the perioperative period, with the addition of troponin, NT-proBNP and creatinine levels on the first, second and fifth postoperative day.

6.4. *Data management*

All participant data will be stored anonymously in an electronic database created explicitly for this trial.

6.5. *Follow-up*

Follow-ups will be conducted by telephone 30 days after randomisation and on the participants' first ambulatory visit after hospital discharge. If the participant or their next of kin cannot be reached, we will use their medical records to obtain the required information. An overview of the outcome assessments is provided in Table 1.

7. Discussion

This trial aims to determine whether a hemodynamic approach using the HPI platform will reduce the rate of hypotension compared to standard APCO monitoring in patients undergoing major abdominal surgery. IH is a risk factor for increased postoperative mortality, myocardial injury, acute kidney failure and perioperative stroke [2–14]. Since the HPI platform was introduced and validated in 2018 [25], few studies have examined its usefulness in different patient populations [23,26–30]. However, these studies focused mainly on comparing the HPI platform with standard hemodynamic management. To our knowledge, three retrospective studies have compared these two hemodynamic monitoring platforms, showing reductions in hypotension episodes with the HPI platform compared to the APCO platform [22,31,32].

A 2021 retrospective study by Grundman [31] examined the rate of hypotension in 100 consecutive adult patients undergoing moderate- or high-risk noncardiac surgery with invasive blood pressure monitoring, of which 50 received hemodynamic monitoring with the FloTrac sensor and 50 with the HPI platform. They demonstrated significant reductions

Table 1
Schedule of enrolment, interventions and assessments. **Specific timepoints listed.

TIMEPOINT**	Enrolment	Study period			
	d_{-1}	Surgical day (d_0)	Daily follow-up (d_0 to d_{hd})	Hospital discharge (d_{hd})	Follow-up (d_{30})
ENROLMENT:					
Eligibility screen	X				
Written informed consent	X				
Written and oral project explanation	X				
Collection of patient demographic and comorbidity data	X				
Allocation		X			
INTERVENTIONS:					
Group A (APCO)		X			
Group B (HPI)		X			
ASSESSMENTS:					
Primary outcomes		X			
Secondary outcomes		X	X	X	X

in the TWA of hypotension below 65 mmHg in the HPI group and the median and cumulative duration of hypotensive events below 65 mmHg for each patient. A 2022 retrospective study by Solares et al. also compared the HPI platform to FloTrac monitoring [22]. They were able to show reductions in the TWA of hypotension <65 mmHg, with a median of 0.09 mmHg in the HPI group and 0.23 mmHg in the FloTrac group, and the duration of hypotensive events relative to the total surgery/monitoring time. A similar retrospective analysis by our group [32] also showed a reduction in the TWA of hypotension <65 mmHg in high-risk patients undergoing major abdominal surgery with HPI compared to APCO hemodynamic monitoring. The patients in the HPI group had fewer hypotensive episodes and spent less time in hypotension than those in the FloTrac group.

Since these retrospective studies, two randomised controlled trials have shown a reduction in hypotension with the HPI platform. One by an Italian group published in 2023 involving 60 patients undergoing major gynaecological oncologic surgery showed a significant reduction in the TWA of hypotension <65 mmHg in the HPI group compared to the APCO group [33]. Unfortunately, like previous studies on the HPI platform, they did not report any secondary outcomes related to postoperative organ injury due to hypotension episodes. A prospective randomised controlled trial by a Japanese group involving 64 adult patients undergoing major noncardiac surgery showed a reduction in hypotension based on the TWA for a MAP of <65 mmHg in the HPI group (0.19 mmHg) compared to the APCO group (0.66 mmHg) [34]. Again, they did not report any data on possible postoperative organ dysfunction in both groups.

However, it is not possible to discuss the issue of the HPI without it's possible limitations and concerns regarding it's true usefulness. A prospective observational study performed on a group of 20 adult patients undergoing living donor liver transplantation showed that the performance of the HPI technology was inferior to the previously reported values in patients undergoing major surgery [35]. Previous studies in noncardiac surgeries showed very good performance of the HPI technology with AUC values greater than 0.95 at 5, 10 and 15 min before the occurrence of hypotension [25]. The AUC value for predicting hypotension with the HPI in patients undergoing living donor liver transplantation at 5 min was 0.810, and for predicting hypotension at 10 and 15 min, 0.726 and 0.689, respectively [35]. There is a correlation between MAP and HPI, described as the mirror effect [36]. When the HPI value reaches 85, which is the default alarm level for the intervention, the corresponding MAP is approximately 72–76 mmHg, so using these values as a treatment trigger might be as beneficial in predicting hypotension as the HPI performance [37]. The similar performance of the HPI and MAP was proved in an observational study published recently, which analysed data from 100 patients undergoing moderate and high risk elective noncardiac surgery. The authors of the study concluded that in clinical practice, the alarms of the HPI are highly similar to those from MAP, with a mean arterial pressure threshold set at 72 or 73 mmHg [38].

In our trial, we would like to compare the utility of HPI monitoring to standard APCO monitoring in high-risk patients undergoing major abdominal surgery. To our knowledge, no similar randomised controlled trials have been published to date. Furthermore, we would like to examine whether the expected reduction in hypotension will transfer to a clinically important reduction in organ complications, such as myocardial injury or kidney failure, as secondary outcomes.

CRediT authorship contribution statement

Jakub Szrama: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Agata Gradys:** Writing – review & editing, Visualization, Project administration, Methodology, Conceptualization. **Zuzanna Nowak:** Writing – review & editing, Investigation, Data curation. **Ashish Lohani:** Writing – review & editing, Investigation, Data curation. **Krzysztof Zwoliński:** Writing – review & editing, Investigation, Data curation. **Tomasz Bartkowiak:** Writing – review & editing, Investigation, Data curation. **Amadeusz Woźniak:** Writing – review & editing, Investigation, Data curation. **Tomasz Koszel:** Writing – review & editing, Investigation, Data curation. **Krzysztof Kusza:** Writing – review & editing, Supervision, Project administration.

Ethical and legal considerations

This trial will be conducted according to the Declaration of Helsinki and in compliance with the protocol and local laws and regulations relevant to the country of conduct. The current version of the study protocol was approved by all competent authorities and by the Bioethics Committee of Poznan University of Medical Sciences (KB–559/220; date 01/07.2022). The trial has been registered in ClinicalTrials.gov (NCT06247384).

Contributions

JS and AG designed the trial. JS, AG and KK offered recommendations and will regularly follow the study. JS and AG drafted the manuscript, while all the authors edited it. JS and AG prepared the hemodynamic protocols. JS estimated the required sample size. JS, AG, ZN, AL, KZ, TB, AW and TK will perform the treatments. All authors have revised and approved the final manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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