

PROTOCOL

Intraoperative implementation of the hypotension probability indicator (HPI) algorithm
a pilot randomized controlled clinical trial

- HYPE TRIAL -

Version 4.0

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
CO	Cardiac Output
dp/dt	A measure of left ventricular contractility from an arterial pressure waveform
DSMB	Data Safety Monitoring Board
Eadyn	Dynamic elastance
EDVI	End-diastolic volume index
EF	Ejection fraction
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
IB	Investigator's Brochure
IC	Informed Consent
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
HLOS	Hospital length of stay
HPI	Hypotension Probability Indicator / Hypotension Probability Index
MAP	Mean arterial pressure
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
PACU	Post Anaesthesia Care Unit
QoR	Quality of recovery

RCT	Randomized controlled trial
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics (in Dutch: officiële productinformatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
SV	Stroke volume
SVV	Stroke volume variation
SVR	Systemic vascular resistance
TWA	Time weighted average
WBP	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgegevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)

SUMMARY

Rationale:

Hypotension during surgery is associated with increased morbidity and mortality. Even short durations of arterial blood pressure below 65 mmHg significantly increased the risk of myocardial ischemia, neurological deficits, renal insufficiency, and mortality (1-4).

Hypotension is common and in a recent study performed in non-cardiac surgical patients in the AMC, we found that up to 60% of patients endured hypotension (defined as mean arterial pressure below 65 mmHg) during anaesthesia for an average of 10% of surgery time (5, 6).

Hypotension is preventable however current management of the hypotensive episodes is predominantly reactive and rather occurs with some delay. A proactive system of hypotension management is needed. Edwards Lifesciences has developed an algorithm using continuous invasively-measured arterial waveforms to predict hypotension with high accuracy minutes before blood pressure actually decreases (5). We hypothesize that the use of this algorithm will alter treatment of hypotension and reduces the amount of hypotension as measured by the time weighted average (TWA) during non-cardiac surgery. This pilot study aims to provide insight into the current treatment of hypotension during surgery and aims to test the diagnostic protocol.

Study design:

This is a pilot study. The study is divided in two parts:

- A. Prospective data collection (baseline data)
- B. Prospective randomized controlled clinical trial (RCT)

Objectives:

Prospective data collection (baseline data)

Objectives:

- What is the time weighted average spent in hypotension (defined as MAP <65 mmHg) during surgery?
- What is normal treatment behaviour of hypotension during surgery? (treatment choice, treatment dose, time to treatment from onset of hypotension/HPI increase)
- What is the time weighted average spent in hypertension (defined as MAP >100 mmHg) during surgery?

RCT phase

Objectives:

- Does availability of HPI together with suggestions of the cause of hypotension change treatment behaviour and correctness of the assessment among anaesthetists and do they alter time towards treating hypotension?
- Can availability of Hypotension Probability Index (HPI) reduce **the time weighted average**, the incidence and the percentage of time spent in hypotension (defined as MAP<65 mmHg) during surgery?
- Does early treatment based on HPI increase the incidence, the TWA and the percentage of time spent in hypertension (defined as MAP >100) during surgery?
- Feasibility of working with HPI (assessed by number of non-treated alarms)
- Explore the relation of HPI alarms to changes in hemodynamic parameters, measured beat-to-beat (CO, SV, SVV, SVR, elastance, dP/dT)
- Can availability of HPI during surgery, reduce the TWA, incidence and percentage of time spent in hypotension (defined as MAP<65 mmHg) after surgery?
After surgery is defined as the period when patients are monitored at the Post Anesthesia Care Unit (PACU), before being discharged to a normal nursing ward.

Study population:

All adult patients requiring an arterial line (*at discretion treating physician*) undergoing non-cardiac non-day surgery with an expected duration of more than 2 hours and an aimed MAP of 65 mmHg.

Intervention (if applicable):

There will be no interventions in the prospective data collection (part A) of this study.

In part B of this study, the RCT, we will randomize the participants into two arms:

- 1) Treatment arm: Flotrac with HPI software. HPI will be calculated via FlotracIQ connected to the radial arterial line. The treating anaesthetist is trained to understand Flotrac parameters and the meaning of HPI. The treating anaesthetist is provided with guidance by means of a flowchart suggesting when to treat and what (see Flow chart in Appendix I). Timing of treatment and choice of treatment is then left to the discretion of the attending physician.

2) Conventional arm: Institutional Standard of Care with an intention to keep MAP > 65 mmHg. The FloTracIQ will be connected to collect data but covered completely. Timing and choice of treatment is left completely to the attending physician.

We look at the effect of introduction of a protocol (*based on FloTracIQ*) with blood pressure targets and predictive analytics to test if it alters treatment behaviour of the anaesthetist during surgery, and if it reduces total length in time spent in hypotension during and after surgery.

Main study parameters/endpoints:

- Does availability of HPI together with suggestions of the cause of hypotension change treatment behaviour and correctness of the assessment among anaesthetists and do they alter time towards treating hypotension?
- Can availability of Hypotension Probability Index (HPI) reduce the time weighted average spent in hypotension (defined as MAP < 65 mmHg) during surgery?
- Can availability of HPI during surgery, reduce the time weighted average spent in hypotension (defined as MAP < 65 mmHg) after surgery?

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

The FlowtracIQ sensor will be connected to the radial arterial line, this provides no extra risks for participants. Validation of HPI in an offline model showed the HPI algorithm predicted hypotension with high sensitivity and specificity minutes before the occurrence of hypotension (5). The study participants allocated to treatment according to de HPI algorithm will receive information on cause of hypotension before hypotension is predicted to occur. Theoretically, early treatment may lead to (transient) hypertension (MAP > 100). Besides transient hypertension no adverse events are expected during this study. The anaesthetist in charge is free to deviate from the HPI algorithm protocol when judged necessary. This study provides no benefits for the participants.

1. INTRODUCTION AND RATIONALE

Intraoperative hypotension occurs often. In a recent not yet published study (5, 6), we found in the AMC that up to 60% of patients endured hypotension (defined as mean arterial pressure below 65 mmHg) during anaesthesia for an average of 10% of surgery time. Hypotension during surgery is associated with increased morbidity and mortality. Studies have shown that even short durations of intraoperative arterial blood pressure below 65 mmHg significantly increased the postoperative risk of myocardial ischemia, neurological deficits, renal insufficiency, and 30-day mortality (1-4).

Not only the time spent in hypotension but also the severity of hypotension is important for associations with postoperative outcome. The time weighted average (TWA) combines the time and depth of hypotension (7) and is therefore a good outcome parameter to study. The TWA calculates the area under the threshold (in this study we use a threshold of 65 mmHg) per unit total time of measurement.

Current treatment of intraoperative hypotensive episodes is not proactive and rather occurs with some delay. There is need for a method to prevent hypotension. Edwards Lifesciences has developed an algorithm that by analysing continuously invasively measured arterial waveforms with the FlotracIQ is able to predict hypotension with high accuracy minutes before blood pressure actually decreases (5). Theoretically this would enable the treating anaesthetist to proactive treat the predicted hypotension and thereby reducing the TWA.

The algorithm developed is named the hypotension probability index (HPI), for example a HPI of 85 translates approximately to a 85% chance of hypotension to occur in the following minutes (unpublished data, see Chapter 6). The secondary screen of the HPI shows variables such as dp/dt, dynamic elastance, systemic vascular resistance as well as stroke volume, cardiac output and stroke volume variation. These variables provide insight in the pathophysiology of the predicted hypotension and in this way enable the treating anaesthetist to provide the correct therapy to prevent this hypotension from occurring. The device Flotrac is CE approved and has been in use in the operation room for years. The FlotracIQ with HPI software is also CE approved but this will be the first clinical study evaluating its possible beneficial effect. In this two-phased trial we will test our hypothesis that the guided use of the HPI will alter hypotension treatment and can reduce the time weighted average spent in hypotension during and after surgery.

2. OBJECTIVES

Study phase A: Prospective Data Collection

Objectives:

- What is the time weighted average spent in hypotension (defined as MAP<65 mmHg) during surgery?
- What is normal treatment behaviour of hypotension during surgery?
(Treatment choice, treatment dose, time to treatment)
- Hemodynamic parameters, measured beat tot beat (CO, SV, SVV, SVR, elastance, dP/dT)
- What is the time weighted average spent in hypertension (defined as MAP>100 mmHg) during surgery?

Study phase B: Prospective randomized controlled clinical trial.

Objectives:

- Does availability of HPI together with suggestions of the cause of hypotension change treatment behaviour and correctness of the assessment among anaesthetists and do they alter time towards treating hypotension?
- Can availability of Hypotension Probability Index (HPI) reduce **the time weighted average**, the incidence and the percentage of time spent in hypotension (defined as MAP<65 mmHg) during surgery?
- Does early treatment based on HPI increase the incidence, the TWA and the percentage of time spent in hypertension (defined as MAP >100) during and after surgery?
- Feasibility of working with HPI (assessed by number of non-treated alarms)
- Explore the relation of HPI alarms to changes in hemodynamic parameters, measured beat-to-beat (CO, SV, SVV, SVR, elastance, dP/dT)
- Can availability of HPI during surgery, reduce the TWA, incidence and percentage of time spent in hypotension (defined as MAP<65 mmHg) after surgery?
After surgery is defined as the period when patients are monitored at the Post Anesthesia Care Unit (PACU), before being discharged to a normal nursing ward.

3. STUDY DESIGN

This study is divided into two parts:

- A. Prospective data collection (3-6 months)
- B. Prospective randomized controlled clinical trial (12 months)

A. Prospective data collection

This will be a baseline data collection. We aim to include 40 patients and we estimate this will take 3 months. We use this phase to be able to correct for the possible Hawthorne effect. We expect a Hawthorne effect during the RCT phase simply because more attention will be drawn to prevent hypotension during surgery.

The baseline data collection enables us to prospectively calculate the time weighted average spent in hypotension and provides data on normal treatment behaviour of anaesthetists in the AMC.

B. RCT

We aim to include 60 patients and we estimate this will take 6 months. This phase consists of a randomized controlled clinical trial in which patient and statistician are blinded. Additionally the treating anaesthetist in the conventional arm is blinded to FlowtracIQ variables. The two study arms are described below:

1) Treatment arm: Flotrac with HPI with guidance. HPI will be calculated via FlotracIQ connected to the radial arterial line. The treating anaesthetist is trained to understand Flotrac parameters and the meaning of HPI. The treating anaesthetist is provided with guidance concerning timing of treatment (HPI >85%) and the causes of hypotension. See flowchart in Appendix I. HPI values above 85 translate to a 85% of hypotension to occur in the following minutes,. HPI values between 50-85% translates approximately to a 50-85% change of hypotension to occur in the following minutes (see chapter 6). When HPI falls in the 50-85% range the study investigator starts diagnosing the cause of pending hypotension via the secondary screen. If HPI reaches 85%, treatment is suggested to be started and the investigator informs the anesthesiologist of the most likely cause of hypotension (see Appendix I) The anesthesiologists treats the patient based on these suggestions but may choose to deviate from the study protocol if deemed necessary in both timing as well as treatment.

Specific scenarios can be formulated with use of the secondary screen. The secondary screen of the FloTracIQ provides the investigator and treating anaesthetist with variables such as dp/dt, dynamic elastance, systemic vascular resistance as well as stroke volume, cardiac output and stroke volume variation. In Appendix II the pathophysiological meaning of these variables is explained. For more information about the FloTracIQ device and or the HPI software please read chapter 5 and chapter 6.

2) Conventional arm: Institutional Standard of Care (excluding perioperative goal directed therapy) with intention to keep MAP > 65 mmHg. The FloTracIQ will be connected but fully covered. We connect the device to be able to calculate the TWA similarly to the intervention group.

In the RCT phase of this study we look at the effect of introduction of a protocol (*based on FloTracIQ*) with blood pressure targets and predictive analytics to reduce total TWA spent in hypotension during surgery.

Hemodynamic monitoring and treatment after surgery:

Before discharge to a normal nursing ward, all patients will be monitored at the post anaesthesia care unit (PACU), according to institutional standard of care. During this phase, all study participants will remain hemodynamically monitored according to institutional standard of care and will receive no extra study interventions. The FloTracIQ will remain connected.

This is a pilot study. We can use this data to set up a larger multicentre study in the future.

4. STUDY POPULATION

4.1 Population (base)

All adult patients requiring an arterial line (*at discretion treating physician*) undergoing non-cardiac non-day surgery with an expected duration of more than 2 hours and an aimed MAP of 65 mmHg

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Aged 18 years or older
- Planned for elective non-cardiac non-day surgery with an expected duration of more than 2 hours
- Planned to receive general anaesthesia
- Planned to receive an arterial line during surgery
- Aim for MAP of 65 mmHg during surgery
- Being able to give written informed consent prior to surgery

4.3 Exclusion criteria

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

- Aim for MAP other than 65 mmHg at discretion treating physician
- Significant hypotension before surgery defined as a MAP <65
- Right- or left sided cardiac failure (e.g. LVEF<35%)
- Known cardiac shunts (significant)
- Known aortic stenosis (severe)
- Severe cardiac arrhythmias including atrial fibrillation
- Requiring dialysis
- Liver surgery
- Vascular surgery with clamping of the aorta
- Perioperative Goal Directed Therapy (PGDT) protocol

4.4 Screen failure

Patients who were planned to receive an arterial line however did not receive an arterial line during surgery will be excluded and can be replaced by a new subject to reach 100 inclusions.

4.5 Technical failure

In the unlikely event data not being stored correctly on the device the patient will be excluded and replaced. This since no TWA data will be present to analyse.

4.6 Patient withdrawal

In the unlikely event a patient will withdraw after the study intervention the patient will be excluded and replaced. This since no TWA data will be available to analyse.

4.7 Sample size calculation

This is a pilot study. A sample size of 30 in each group in the RCT phase will have 80% power to detect an effect size of 0,740 using a two group t-test with a 0,050 two-sided significance level.

The sample size calculation is based on the primary endpoint *time weighted average* (TWA). TWA is a calculation of the depth (in mmHg) of hypotension below the 'threshold' MAP of 65 mmHg x the time spent in hypotension in minutes, this results in an 'area'. To better compare this value between different operations the 'area' can be divided by the total duration of the operation.

To elaborate:

TWA= depth hypotension below 'threshold' in mmHg x time spent in hypotension in minutes. Example: MAP of 50 mmHg for 5 minutes results in a TWA of 75.

TWA= (depth hypotension below 'threshold' in mmHg x time spent in hypotension in minutes) / total duration operation in minutes.

Example: MAP of 50 mmHg for 5 minutes results in a TWA of 75), total duration of operation in minutes is 120 minutes= $75/120=0,625$

Details sample size calculation:

We estimated that a difference of 0,38 or larger for TWA MAP drop under 65 mmHg between two study groups to be clinically relevant. We have calculate an effect size of 0,74 by dividing the estimated difference of 0,38 (mean experimental group – mean control group) by the standard deviation of 0,51. The effect size is used to calculate the sample size with at least a power of 80%.

```
pwr.t.test(n = 30, d = 0,74, sig.level = 0,05, power = NULL, type = c("two.sample"),
alternative = c("two.sided"))
```

Two-sample t test power calculation

n = 30

d = 0,74

sig.level = 0,05

power = 0,8046348

alternative = two.sided

NOTE: n is number in *each* group

Arguments

n	Number of observations (per sample)
d	Effect size
sig.level	Significance level (Type I error probability)
power	Power of test (1 minus Type II error probability)
type	Type of t test : one- two- or paired-samples

Calculated in R

R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>.

Expected loss of data:

If data is missing due to the patient not receiving an arterial line (screen failure), or data not being stored on the device (technical failure) or withdrawal from the patient the data will be excluded and replaced.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

We look at the effect of introduction of a protocol (*based on FloTracIQ*) with blood pressure targets and predictive analytics (HPI) to reduce the time weighted average (TWA) spent in hypotension during and after surgery.

Flotrac device is a CE certified product, in use in European theatres and Intensive Care Units (8, 9). It is used to monitor hemodynamic parameters derived from waveforms, such as cardiac output, stroke volume, stroke volume variation and dynamic elastance. We do not use it outside the scope of the intended use.

Using the Flotrac device means attaching the device to the arterial line, it does not induce any harm or risks for the participants. The Flotrac is completely safe to use.

In our centre the Flotrac device without HPI software is already in use when cardiac output needs to be monitored.

The FloTracIQ device with HPI (hypotension probability index) software is our investigational product (10). The HPI is able to predict hypotension before it occurs, i.e. a HPI of 85 translates approximately to a 85% chance of hypotension to occur in the following minutes (see unpublished data in chapter 6). The variables in the secondary screen (appendix II) provide information on the pathophysiology of the predicted hypotension. Broadly, hypotension can be explained by a preload, afterload or contractility 'problem'. Or otherwise stated, the treatment of hypotension can consist of: fluids, vasopressor and/or inotropes. The variables given by the FloTracIQ HPI are dp/dt , dynamic elastance (E_{dyn}), stroke volume (SV), stroke volume variation (SVV), cardiac output (CO) and systemic vascular resistance (SVR). By knowing the values of these variables the anaesthetist can 'diagnose' the cause of the hypotension and thereby administer the correct treatment.

We use the FloTracIQ device HPI ***additionally*** to conventional intraoperative monitoring. Furthermore the treatment suggestions we will provide is not different from the standard treatment options used to treat intraoperative hypotension.

The difference, however, can be found in treating the hypotension proactive rather than reactive. See appendix I for the treatment and guidance flow diagram.

We aim to test if guided use of the HPI will alter hypotension treatment and can reduce the time weighted average spent in hypotension during, and after surgery.

the HPI is CE certified (11) and has been validated on prospectively collected patient data by means of offline analysis (5), however this will be the first clinical trial in humans.

5.2 Use of co-intervention (if applicable)

Not applicable.

5.3 Escape medication (if applicable)

We will study if hypertension is occurring more often in the treatment group. Hypertension will be treated by the treating anesthetist with reduction in vasopressor dose, vasodilators, or increasing depth of anesthesia as is normal practice.

6. INVESTIGATIONAL PRODUCT

The FlotraclQ HPI has a CE mark (11). We will use the product within the indication. Specific instructions for use can be found in the product brochure online (10).

6.1 Name and description of investigational product(s)

FlotraclQ Hypotension Probability Indicator (HPI) notifies the clinician when the Hypotension Probability parameter reaches a pre-set upper threshold.

The HPI value will update every 20 seconds and displays as a percentage equating to the probability that a hypotensive event may occur. The higher the percentage value, the higher the likelihood that a hypotensive event will occur.

When the HPI value exceeds 85%, a high priority alarm indicates to the user that a patient may be trending towards a hypotensive event (MAP < 65 mmHg). This includes an alarm tone, red parameter status color, and flashing parameter value. Which will be covered (screen) or switched off (alarm) in the control group.

A HPI value of 85% translates to approximately a 85% chance of hypotension to occur in the following minutes:

HPI (%)	Event Rate (%)	Time (min), Median, [10 th , 90 th percentile]
50-54	43.4	7.7 [2.7, 13.3]
55-59	44.3	7.3 [3.0, 13.1]
60-64	57.0	6.7 [2.7, 12.8]
65-69	56.8	5.7 [2.3, 12.3]
70-74	67.2	5.7 [2.0, 11.7]
75-79	81.0	4.7 [2.0, 11.0]
80-84	84.2	5.0 [1.7, 12.3]
85-89	92.9	4.0 [1.7, 10.3]
90-94	95.8	3.7 [1.3, 10.0]
95-99	97.6	1.3 [0.3, 8.0]

Figure 1: HPI value, event rate and median time to event. Nonpublished data, confidential.

Furthermore a high alert popup appears recommending a review of the patient hemodynamics. Hemodynamic information associated with hypotension is available for the user on the HPI Secondary Screen. That information includes several key parameters (MAP, CO, SVR, SV, SVV, dP/dt, Eadyn) as indicators of preload, contractility, and afterload.

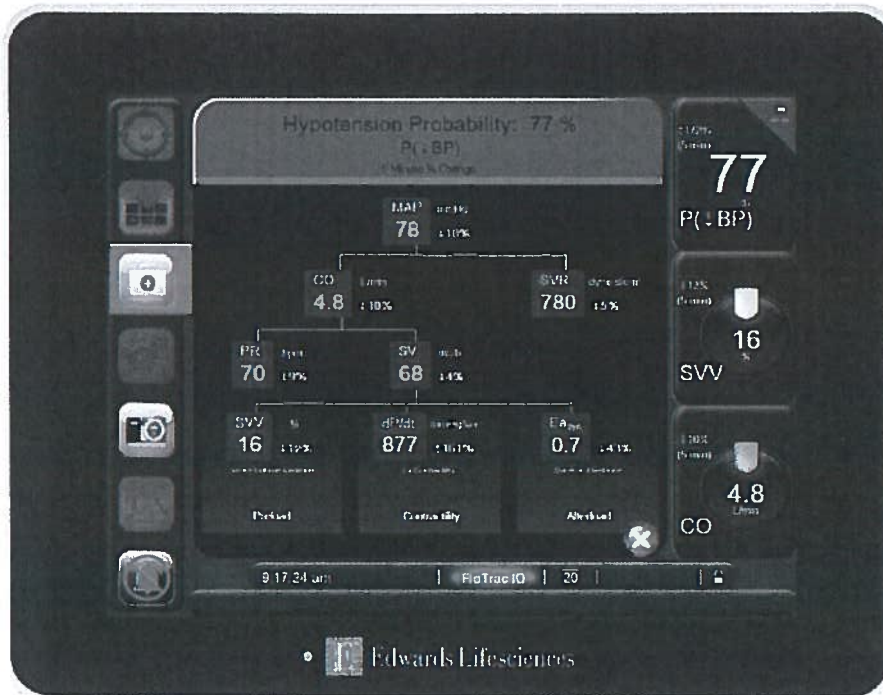


Figure 2: Secondary screen. See Appendix II for more information on the secondary screen.

6.2 Summary of findings from non-clinical studies

The performance of the HPI was assessed in a porcine model (not published data, confidential). This animal study examined the HPI in a hemorrhagic model and a vasodilation translational model to estimate the probability of a hypotension event in the acute setting. Swine were intubated with arterial lines and pulmonary artery catheters were placed to measure right heart cardiovascular parameters and continuous cardiac output (CO). Five swine were bled by venous catheter 5-20 cc/min after establishing baseline stabilization. Animals were bled to MAP of 60mm/hg and sustained for 15 min and fluid resuscitated via auto transfusion to MAP of 85mm/hg for 30 min. Then hypotension was induced by infusion of Nitroprusside to reduce MAP less than 65mm/hg for 15 min.

The two models create hypotension in distinct modalities.

- The hemorrhage model directly reduces blood volume, demonstrating the direct relationship between hypotension probability and reduction in optimal fluid status. This model directly analyzes the ability of HPI to demonstrate the probability of an acute event with the reduction in left ventricular volume.
- The vasodilation model, by the use of a vasodilation substance, demonstrates the direct effect of afterload reduction and the relationship to HPI.

In both models, mean arterial pressure (MAP), hypotension probability indicator (HPI), heart rate (HR), stroke volume variation (SVV), dP/dt, arterial dynamic elastance (Eadyn), stroke volume (SV), systemic vascular resistance (SVR), end-diastolic volume index (EDVI), and ejection fraction (EF) were measured.

Both models show that the mathematical analog demonstrates the absolute usefulness in using the dynamic changes in ventricular force compared to the ability of the vascular vessels to increase tone. As dP/dt acutely increases, cardiac performance compensates maximally thus maintaining mean arterial pressure. Eventually dP/dt will decrease as Eadyn increases which is reflected as an increase in HPI showing a high probability of an acute hypotension event.

In short, the hemorrhage model demonstrates the ability of HPI to use arterial waveform analysis to analyze the left ventricular performance and arterial tone to give a reliable probability for a hypotensive episode. The vasodilation model demonstrated the usefulness of the HPI in measuring the probability of an acute hypotensive event with dynamic left cardiac forces interacting with arterial tone.

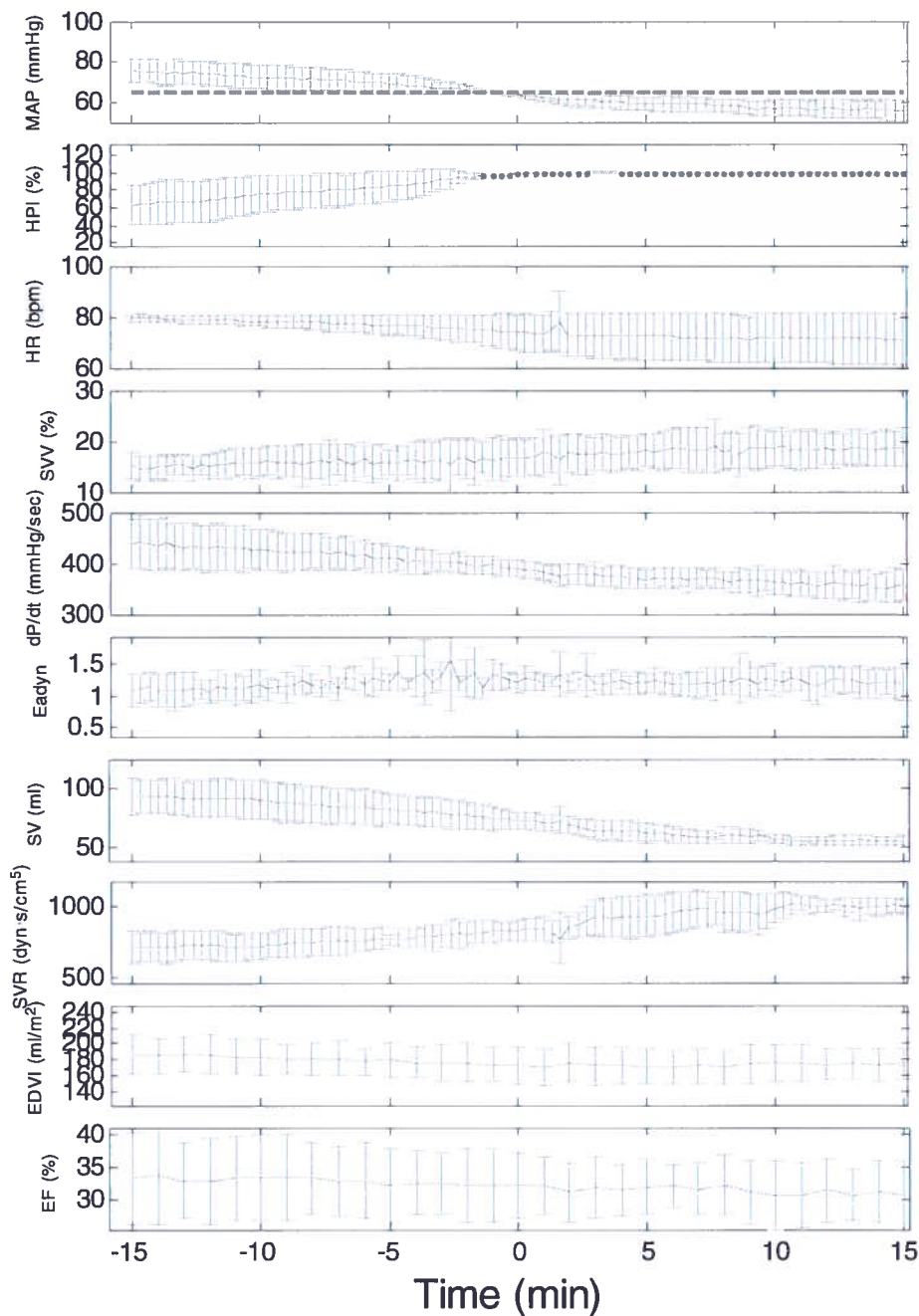


Figure 3: mean \pm std value of vital signs and hemodynamic parameters in the hemorrhage model for all animals before and after 15 minutes of hypotension. Time 0 is the time when hypotension happens. From top to bottom: mean arterial pressure (MAP), hypotension probability indicator (HPI), heart rate (HR), stroke volume variation (SVV), dP/dt, arterial dynamic elastance (Eadyn), stroke volume (SV), systemic vascular resistance (SVR), end-diastolic volume index (EDVI), and ejection fraction (EF). The pink dashed line at the top graph shows the mark for 65 mmHg.

6.3 Summary of findings from clinical studies

The HPI was developed on an offline clinical dataset of 293 patients, of which 97 patients in theatre and 196 ICU patients. HPI validation was performed in 350 randomly selected patients from clinical databases, 298 were ICU patients and 52 were patients in theatre.

The HPI encompasses 23 waveform characteristics such as the slope of the curve. These 23 characteristics were found to predict hypotension using machine-learning techniques. Logistic regression was used, this is a modeling method for predicting the probability of a binary response based on one or more predictor features. It has the benefit of generating a numerical score to reflect the degree of the severity in the patient. This is achieved by using the 'logit' transformation of the dependent binary variable and conducting a linear regression. The exact variables used in the HPI algorithm are not made public and are considered confidential.

Validation of HPI in an offline model, based on anonymized patient data from our centre (AMC) showed the HPI algorithm predicted hypotension with high sensitivity and specificity (5). In 160 patient undergoing surgery a total of 834 hypotensive events were registered. The HPI algorithm was able to predict hypotension with a sensitivity of 92%, 89% and 87%, and a specificity of 92%, 89% and 87%, 5 mins, 10 mins and 15 mins prior to the event respectively.

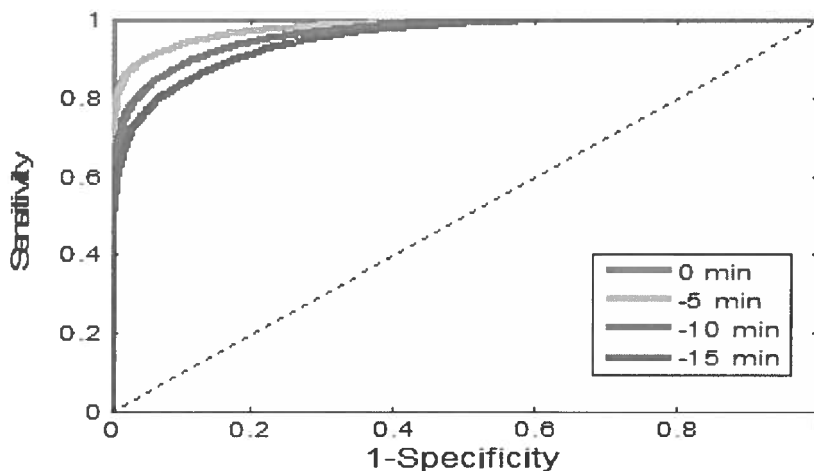


Figure 4: Reliability of the hypotension probability indicator (HPI) to predict a hypotensive event in time prior to the event. *Veelo et al, ASA conference, 2016 (5)*

The software is CE approved and already on the European market available for use in humans.

6.4 Summary of known and potential risks and benefits

The FlotraclQ sensor will be connected to the radial arterial line, this provides no extra risks for participants. The study participants allocated to treatment according to de HPI algorithm will receive diligently titrated vasopressors, inotropes or fluids minutes before hypotension is predicted to occur. Theoretically this may lead to (transient) hypertension (MAP>100), but this risk is also present in the control group and is inherent to the use of vasopressors. Besides transient hypertension no adverse events are expected during this study. The anaesthetist in charge is free to deviate from the HPI algorithm protocol when clinically necessary.

6.5 Description and justification of route of administration and dosage

Not applicable

6.6 Dosages, dosage modifications and method of administration

Not applicable

6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable

6.8 Drug accountability

Not applicable

7. NON-INVESTIGATIONAL PRODUCT**7.1 Name and description of non-investigational product(s)**

Not applicable.

7.2 Summary of findings from non-clinical studies

Not applicable.

7.3 Summary of findings from clinical studies

Not applicable.

7.4 Summary of known and potential risks and benefits

Not applicable.

7.5 Description and justification of route of administration and dosage

Not applicable.

7.6 Dosages, dosage modifications and method of administration

Not applicable.

7.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable.

7.8 Drug accountability

Not applicable.

8. METHODS

8.1 Study parameters/endpoints

Phase A: Prospective data collection

8.1.1 Main study parameters/endpoints

- Time weighted average spent in hypotension (defined as MAP<65 mmHg) during surgery
- Incidence of hypotension (defined as MAP<65 mmHg) during surgery
- Time spent in hypotension (defined as MAP<65 mmHg) during surgery
- Treatment choice
 - *amount of vasopressor during surgery
 - *amount of inotrope during surgery
 - *amount of fluids during surgery
- Treatment dose
- Time to treatment
- Diagnostic guidance protocol deviations
- Hemodynamic parameters, measured beat tot beat (CO, SV, SVV, SVR, elastance, dP/dT)
- Percentage of time in hypertension (defined as MAP >100 mmHg) during surgery?
- Incidence of hypertension (defined as MAP >100 mmHg) during surgery?
- TWA spent in hypertension (defined as MAP>100 mmHg) during surgery?
- Hemodynamic parameters, measured beat tot beat (CO, SV, SVV, SVR, elastance, dP/dT)

Phase B: RCT

8.1.2 Main study parameters/endpoints

We compare a group with access to HPI and access to FlotracIQ parameters (CO, SV, SVR, SVV, dynamic elastance, dP/dT, see appendix II) to a group treated according to institutional standard care.

- Time weighted average spent in hypotension (defined as MAP<65 mmHg) during and after surgery
- Incidence of hypotension (defined as MAP<65 mmHg) during and after surgery
- Time spent in hypotension (defined as MAP<65 mmHg) during and after surgery
- Treatment choice
 - *amount of vasopressor during and after surgery
 - *amount of inotrope during and after surgery
 - *amount of fluids during and after surgery
- Treatment dose
- Time to treatment
- Diagnostic guidance protocol deviations
- Hemodynamic parameters, measured beat tot beat (CO, SV, SVV, SVR, elastance, dP/dT)
- Percentage of time in hypertension (defined as MAP >100 mmHg) during and after surgery?
- Incidence of hypertension (defined as MAP >100 mmHg) during and after surgery?
- TWA spent in hypertension (defined as MAP>100 mmHg) during and after surgery?

8.2 Randomisation, blinding and treatment allocation

Phase A: Prospective data collection:

No randomisation, no blinding.

Phase B: RCT

Patients are randomly allocated (1:1) to HPI or standard treatment. Randomisation is done centrally using a web-based randomisation module Computer-generated permuted block randomisation with a 1:1 allocation ratio and concealed varying permuted block sizes of two, four, six patients will be used. The patient and statistician are blinded. Additionally the treating anesthetist in the conventional arm is blinded to FlowtracIQ variables, The FlotracIQ will be connected but fully covered. Because of the nature of the interventions, the investigators were not masked to group allocation.

8.3 Study procedures

Phase A: Prospective data collection

Study population:

Adult patients requiring an arterial line undergoing non-cardiac non-day surgery with an expected duration of more than 2 hours and an aimed MAP of 65 mmHg without any exclusion criteria will be studied after patient's informed consent is obtained.

Data collection:

Data will be collected prospectively. Intra-operative hypotension is defined as arterial line derived MAP <65 mmHg after surgical incision. This because in our academic centre the arterial line is often placed after induction. Data will be collected from 15 minutes after induction until the end of surgery. Study data will be saved anonymised, only using the anonymised study number, on the FlotracIQ. This anonymised data will be extracted from the FlotracIQ using a secured USB stick. This USB stick is stored in a designated area. In the AMC this will be in the room of Denise Veelo, in a lockable closet. Data extraction from the FlotracIQ will be done by selected team members from each institute which will be clearly stated on the delegation log. Electronical patient database (EPD) derived data will be anonymised after extraction. EPD data extraction will be performed by selected study team member only which will be clearly stated on the delegation log.

The data will be stored anonymized onto the hospital (AMC computer network at an appropriate sub-directory only accessible by the study team named in the site signature and delegation log).

Phase B: RCT

Study population:

Adult patients requiring an arterial line undergoing non-cardiac non-day surgery with an expected duration of more than 2 hours and an aimed MAP of 65 mmHg without any exclusion criteria will be studied after patient's informed consent is obtained.

Data collection:

In both the intervention and control group peri-operative hypotension data collection (arterial line derived MAP <65 mmHg) will start 15 minutes after induction (excluding post-induction hypotension). This because in our academic centre the arterial line is often placed after induction. Data collection stops when the patient is discharged to a normal nursing ward. Study data will be saved anonymised, only using the anonymised study number, on the FlotracIQ. This anonymised data will be extracted from the FlotracIQ using a secured USB stick, locked with pin code. This USB stick is stored in a designated area. In the AMC this will be in the room H1-134, in a lockable closet. Data extraction from the FlotracIQ will be done by selected team members from each institute which will be clearly stated on the delegation log. Electronical patient database (EPD) derived data will be anonymised after extraction. EPD data extraction will be performed by selected study team member only which will be clearly stated on the delegation log. The data will be stored anonymized onto the hospital (AMC) computer network at an appropriate sub-directory only accessible by the study team named in the site signature and delegation log. The key to the randomisation will be kept at the AMC.

*Hemodynamic monitoring and treatment during surgery:*Control group:

The study participants randomised to be hemodynamically monitored according to institutional standard of care will receive no study interventions during surgery. The anesthesiologist initiates treatment and timing of treatment according to standard practice and insight.

Intervention group:

The study participants randomised to the FlotracIQ HPI arm will have a Flotrac connected to the arterial line in theatre. The treating anaesthetist is trained to understand Flotrac parameters (CO, SV, SVR, SVV, elastance, dP/dT, see appendix II) and the meaning of HPI.

A HPI of 85 translates approximately to a 85% chance of hypotension to occur in the following minutes. By interpreting the FlotracIQ parameters the treating anaesthetist is able to diagnose the cause of the predicted hypotension. Broadly, hypotension can be caused by a preload, contractility or afterload problem and the subsequent treatment options are fluids, inotropes or vasopressor; or a combination. This is basic knowledge for

every anaesthetist and every anaesthesiology assistant (nurse). Furthermore the treating anaesthetist is provided with a diagnostic flowchart (see appendix I) for specific scenario's based on the above described well known preload, contractility and afterload concept. The investigator alerts the anesthesiologist if treatment should start according to the protocol and the likely cause of hypotension is discussed. The treating anesthesiologist will then decide whether treatment will be initiated according to plan and which treatment is most appropriate.

Before discharge to a normal nursing ward, all patients will be monitored at the post anaesthesia care unit (PACU), according to institutional standard of care. During this phase, all study participants will remain hemodynamically monitored according to institutional standard of care and will receive no extra study interventions. The FlotracIQ will remain connected.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable

8.5 Replacement of individual subjects after withdrawal

Subjects will be replaced after withdrawal to reach 100 inclusions.

In the unlikely event of data not being stored correctly on the FlotracIQ device or other technical difficulties, subjects can be replaced to reach 100 inclusions.

Patients who were planned to receive an arterial line however did not receive an arterial line during surgery (screen failure) will be excluded and can be replaced by a new subject to reach 100 inclusions.

8.6 Follow-up of subjects withdrawn from treatment

No follow-up will be performed in subjects withdrawn from treatment unless an adverse event directly related to this study occurred.

8.7 Premature termination of the study

We do not expect any serious adverse events directly related to this study. The only adverse event that might be expected is transient hypertension (MAP>100), which also is expected to occur in the standard treatment group. Therefore, we do not expect to have to terminate this study prematurely. Furthermore by treating predicted hypotension proactively we can probably limit the extent (total dose) of treatment necessary and thus diminish iatrogenic induced hypotension.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAEs: adverse events due to surgical complications and complication due to anaesthesiology such

as anaphylactic reactions and desaturations unrelated to our study protocol will not be reported.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

A risk assessment was performed using the 'Risk Assessment in Clinical Research' tool, developed by the AMC-CRU. The final risk classification was 'Moderate Risk'.

Although the device is CE approved and will be used within the indication it is one of the first clinical studies using HPI, therefore we scored it as Moderate Risk.

The FlowtracIQ sensor will be connected to the radial arterial line, this provides no extra risks for participants. The study participants allocated to treatment according to de HPI algorithm will receive diligently titrated vasopressors, inotropes or fluids minutes before hypotension is predicted to occur. These treatment options are not different to conventional therapy. Theoretically, proactive treatment may lead to (transient) hypertension (MAP>100). However, by treating predicted hypotension proactively we can probably limit the amount of treatments use, thereby possibly diminishing iatrogenic induced hypertension.

Besides hypertension no adverse events are expected during this study. The anaesthetist in charge is free to deviate from the HPI algorithm protocol.

Because besides transient hypertension no adverse events are expected during this study we will not establish a DSMB nor monitoring. The use of the FlotracIQ HPI is considered to be safe.

10. STATISTICAL ANALYSIS

An intention to treat analysis will be performed. In the case of the patient not receiving an arterial line during surgery (screen failure) the patient will be excluded and replaced.

Phase A: Prospective data collection

10.1 Primary study parameters/endpoints

- Time weighted average spent in hypotension (defined as MAP<65 mmHg) during surgery
- Incidence of hypotension (defined as MAP<65 mmHg) during surgery
- Time spent in hypotension (defined as MAP<65 mmHg) during surgery
- Treatment choice
 - *amount of vasopressor during surgery
 - *amount of inotrope during surgery
 - *amount of fluids during surgery
- Treatment dose
- Time to treatment
- Diagnostic guidance protocol deviations
- Hemodynamic parameters, measured beat tot beat (CO, SV, SVV, SVR, elastance, dP/dT)
- Percentage of time in hypertension (defined as MAP >100 mmHg) during surgery?
- Incidence of hypertension (defined as MAP >100 mmHg) during surgery?
TWA spent in hypertension (defined as MAP>100 mmHg) during surgery?
- Hemodynamic parameters, measured beat tot beat (CO, SV, SVV, SVR, elastance, dP/dT)

Phase B: RCT

10.2 Primary study parameters/endpoints

We compare a group with access to HPI and access to FlotracIQ parameters (CO, SV, SVR, SVV, dynamic elastance, dP/dT, see appendix II) to a group treated according to institutional standard care.

- Time weighted average spent in hypotension (defined as MAP<65 mmHg) during and after surgery
- Incidence of hypotension (defined as MAP<65 mmHg) during and after surgery
- Time spent in hypotension (defined as MAP<65 mmHg) during and after surgery
- Treatment choice
 - *amount of vasopressor during and after surgery
 - *amount of inotrope during and after surgery
 - *amount of fluids during and after surgery
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- Time to treatment
- Diagnostic guidance protocol deviations
- Hemodynamic parameters, measured beat tot beat (CO, SV, SVV, SVR, elastance, dP/dT)
- Percentage of time in hypertension (defined as MAP >100 mmHg) during and after surgery?
- Incidence of hypertension (defined as MAP >100 mmHg) during and after surgery?
TWA spent in hypertension (defined as MAP>100 mmHg) during and after surgery?
- Hemodynamic parameters, measured beat tot beat (CO, SV, SVV, SVR, elastance, dP/dT)

10.3 Interim analysis (if applicable)

No interim analysis will be performed during one of the study phases.

This study design consists of two phases. In phase A we will conduct a prospective data collection study and in phase B we will convert to a RCT.

10.4 Statistical analysis plan

Continuous normally distributed variables will be expressed by their mean and standard deviation or when not normally distributed as medians and their interquartile ranges.

Categorical variables will be expressed as n (%).

In general, to test groups Student's *t*-test will be used, if continuous data is not normally distributed the Mann-Whitney *U* test will be used. Categorical variables will be compared with the Chi-square test or Fisher's exact tests.

Time Weighted Average is calculated by the summation of the lowest mm-Hg value per time unit (minutes) a patient is in hypotension (< 65 mm-Hg).

As expected TWA and other time related measurements will be most likely show skewed distributions. Besides the visual inspection of the data by histograms and QQ plots we will use the Box Cox procedure for choosing the most appropriate transformation given the data (12).

A logistic regression model will be used to investigate the difference of the incidence of hypotension episodes (< 65 mm-Hg) between groups. The primary determinant will be the randomization groups (HPI used/HPI hidden). The goal of this analysis is to quantify the net effect of the application of the HPI monitor on the incidence of hypotension episodes during surgery, controlling for other variables. Exploration of interaction (effect modification) and confounding is considered methodologically relevant. We will first focus on the crude (uncorrected) effect of the HPI (independent variable) on the incidence of hypotension (dependent variable). Then statistical and clinically relevant covariates will be added as possible interaction terms. As a significant interaction is not found, the model will be examined for confounding. Confounding is defined as $\geq 10\%$ change in the coefficient of the central determinant (HPI use) as a consequence of adding a covariate.

Statistical significance was considered to be at $p 0.05$ (two sided). When appropriate, statistical uncertainty is expressed by the 95% confidence levels.

11. ETHICAL CONSIDERATIONS

11.4 Regulation statement

The study will be *conducted according to the principles of the Declaration of Helsinki (Version October 2013 and in accordance with the Medical Research Involving Human Subjects Act (WMO))*.

This protocol of this study will be submitted to the Medical Ethics Committee of the Academic Medical Centre in Amsterdam. The study will not commence before formal approval has been granted.

11.5 Recruitment and consent

Consent will be obtained at least one day prior to surgery. Consent will be obtained by trained study staff named in the site signature and delegation log. Patients are free to stop participation in the study at any time.

11.6 Objection by minors or incapacitated subjects (if applicable)

No minors and/or incapacitated adults will be participating in this study.

11.7 Benefits and risks assessment, group relatedness

No minors and/or incapacitated adults will be participating in this study.

11.8 Compensation for injury

The chance of injury as a result of the study is very small since the use of FlotracIQ HPI is additional to standard intraoperative monitoring. The treatment we use is not different from the normally used treatment for intraoperative hypotension (vasopressor, inotropes, fluids). We expect this study to make intraoperative care more safe. Not causing any injury.

The sponsor (AMC) has a liability insurance which is in accordance with article 7 of the WMO. This liability insurance is only applicable to the AMC.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study for study subjects in the AMC.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.9 Incentives (if applicable)

There will be no incentives, compensation or treatment that subjects will receive through participation in the study.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.4 Handling and storage of data and documents

The data will be handled confidentially. The patient data will be retrieved from the hospital patient information systems which safeguards the confidentiality of the personal data. The pertinent study data collected will be retrieved from these information systems and entered into appropriate software for subsequent analyses. All data will be anonymised. These data will be stored onto the hospital (Amsterdam) computer network at an appropriate sub-directory only accessible by the study team named in the site signature and delegation log. Any data that leaves the AMC premises will be de-identified. The randomisation key is kept at the AMC. Any publication arising from this study will not contain data that can be traced to a specific patient.

The Principal investigator is responsible for handling and storage of data and documents on their side.

12.5 Monitoring and Quality Assurance

We did not organise monitoring of the study since HPI has a CE mark and thus safe to us. Furthermore we test a diagnostic guidance protocol. We do not force study procedures.

A risk assessment was performed using the 'Risk Assessment in Clinical Research' tool, developed by the AMC-CRU. The final risk classification was 'Moderate Risk'.

The device is CE approved and will be used within the indication. However since it is one of the first clinical studies using HPI we scored it as Moderate Risk.

12.6 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.7 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.8 Temporary halt and (prematurely) end of study report

<The following text is applicable for studies without an investigational medicinal product.>

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.9 Public disclosure and publication policy

The trial will be registered in an international trial registry before the first study patient is recruited. Results of this study will be submitted for publication in a peer reviewed scientific medical journal. No results of this study can be submitted for publication without the written consent of the Academic Medical Center Amsterdam.

13. STRUCTURED RISK ANALYSIS

The FlowtracIQ sensor will be connected to the radial arterial line, this provides no extra risks for participants. The study participants allocated to diagnosis according to de HPI algorithm will receive diligently titrated vasopressors, inotropes or fluids minutes before hypotension is predicted to occur. These treatment options are not different to conventional therapy. Theoretically this may lead to (transient) hypertension (MAP>100). Besides hypertension no adverse events are expected during this study. The anaesthetist in charge is free to deviate from the HPI algorithm protocol when he/she feels necessary.

13.4 Potential issues of concern

*For registered products to be used within the indication and **not** in combination with other products chapter 13.1 can be skipped; explain in chapter 13.2 why 13.1 is skipped >*

The FlotracIQ device is a CE certified product used in clinical care in Europa(8, 9). The HPI software (to use in combination with FlotracIQ) received CE approval October 2016 (11). We use the device within the indication. The hypotension index predictor (HPI) is an algorithm developed using machine learning and validated on an offline model. Preliminary data from this offline model showed the HPI algorithm predicted hypotension with high sensitivity and specificity minutes before the occurrence of hypotension (5).

13.5 Synthesis

The study participants allocated to diagnosis according to de HPI algorithm will receive diligently titrated vasopressors, inotropes or fluids minutes before hypotension is predicted to occur. Theoretically this may lead to (transient) hypertension (MAP>100). Besides hypertension no adverse events are expected during this study. The anaesthetist in charge is free to deviate from the HPI algorithm protocol suggestions when he/she feels necessary. Monitoring with Flotrac HPI is used additionally to standard monitoring. We use the CE approved Flotrac HPI device within the intended indication of use. Therefore the risks for study participants are expected to be low.

14. AMENDMENTS

14.1 Amendment 1 (28-02-2018)

During phase B of the study, data collection will be extended until the study participant is discharged to the normal nursing ward. This entails collection of data only. No study interventions will be performed. HPI will not be used in this postoperative period.

Explanation:

Before discharge to a normal nursing ward, all post-operative patients are monitored at the post anaesthesia care unit (PACU), according to institutional standard of care. During PACU stay we would like to continue data collection, meaning the FlotraclQ will remain connected. This will not lead to risk for the study participants. It will enable us to study if intraoperative use of the HPI results in hemodynamically 'better' patients postoperatively. In other words, we will study if the effect of the use of the HPI algorithm intraoperatively will lead to less hypotension postoperatively.

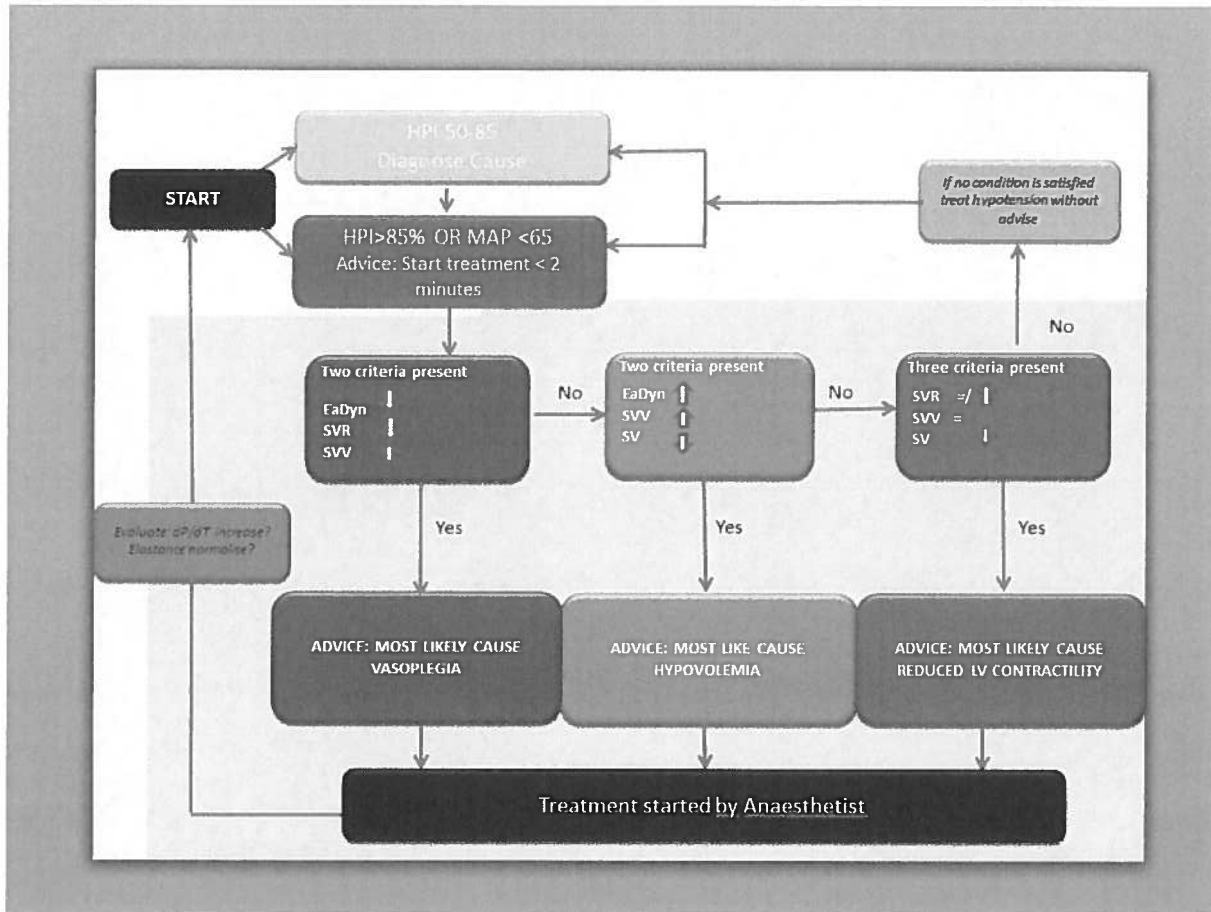
During Phase B of the study, the following extra study parameters will be collected.

- Time weighted average spent in hypotension (defined as MAP<65 mmHg) after surgery
- Incidence of hypotension (defined as MAP<65 mmHg) after surgery
- Time spent in hypotension (defined as MAP<65 mmHg) after surgery
- Time weighted average spent in hypertension (defined as MAP>65 mmHg) after surgery
- Incidence of hypertension (defined as MAP>65 mmHg) after surgery
- Time spent in hypertension (defined as MAP>65 mmHg) after surgery
- Treatment choice
 - *amount of vasopressor after surgery
 - *amount of inotrope after surgery
 - *amount of fluids after surgery

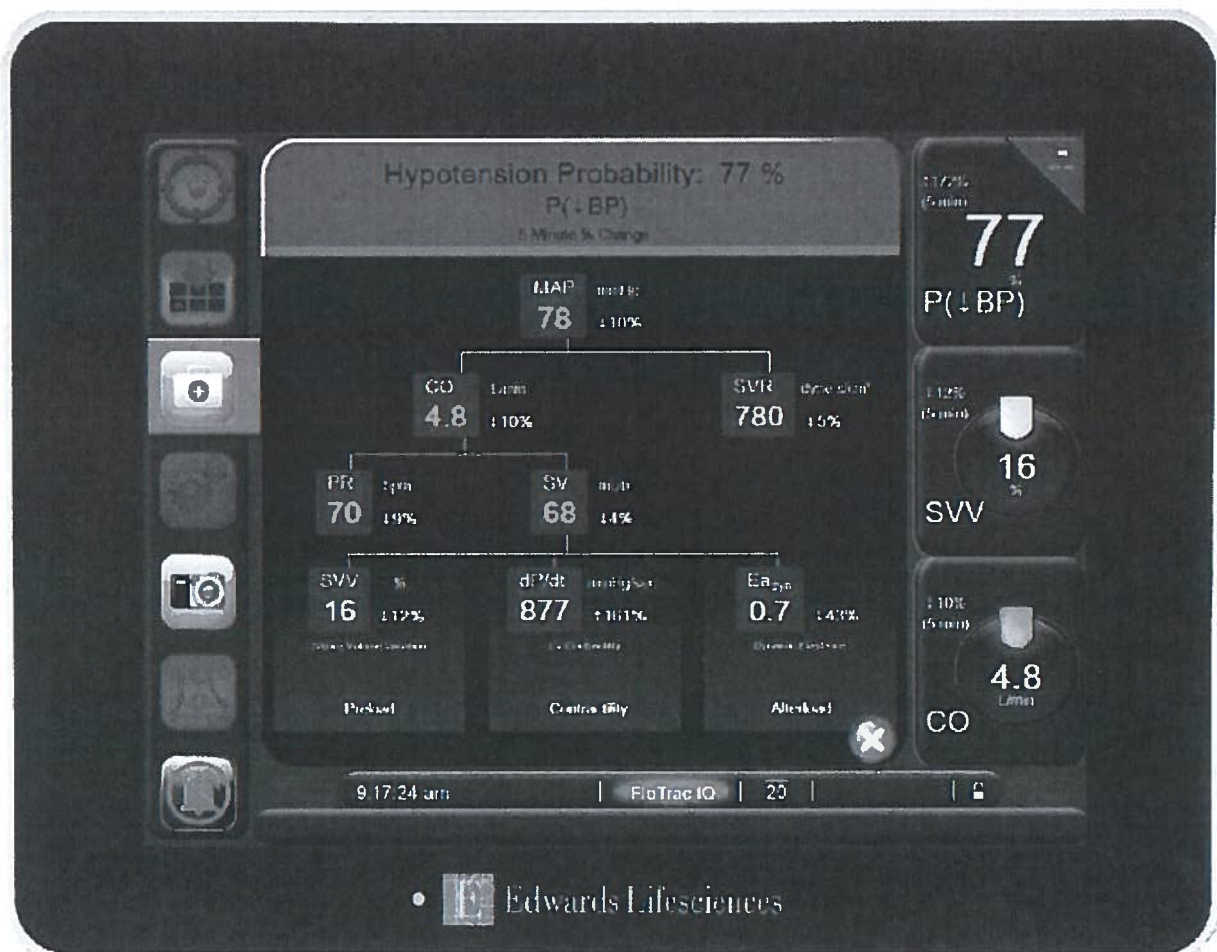
15. REFERENCES

1. Bijker JB, Persoon S, Peelen LM, Moons KG, Kalkman CJ, Kappelle LJ, et al. Intraoperative hypotension and perioperative ischemic stroke after general surgery: a nested case-control study. *Anesthesiology*. 2012;116(3):658-64.
2. Salmasi V, Maheshwari K, Yang D, Mascha EJ, Singh A, Sessler DI, et al. Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery: A Retrospective Cohort Analysis. *Anesthesiology*. 2016.
3. Sun LY, Wijeyesundera DN, Tait GA, Beattie WS. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. *Anesthesiology*. 2015;123(3):515-23.
4. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology*. 2013;119(3):507-15.
5. Veelo D ZJ, Settels J, Hatib F, Hollmann M, Geerts B. Prediction of Hypotensive Episodes With Noninvasive Continuous Waveform Analysis ASA Abstract, A3053 2016.
6. Geerts BF LC, Settels JJ, Hatib F, Hollmann MW, Veelo DP. Noninvasive continuous blood pressure monitoring facilitates earlier detection of hypotensive events during surgery. ASA Abstract, 2016.
7. Hsieh JK, Dalton JE, Yang D, Farag ES, Sessler DI, Kurz AM. The Association Between Mild Intraoperative Hypotension and Stroke in General Surgery Patients. *Anesthesia and analgesia*. 2016;123(4):933-9.
8. Slagt C, Malagon I, Groeneveld AB. Systematic review of uncalibrated arterial pressure waveform analysis to determine cardiac output and stroke volume variation. *British journal of anaesthesia*. 2014;112(4):626-37.
9. <http://www.edwards.com/eu/products/mininvasive/pages/flotracsensor.aspx>.
10. http://ht.edwards.com/scin/edwards/eu/sitecollectionimages/edwards/eu%20hpi%20brochure_digitalversion_largerfile%20for%20online%20use_10-6.pdf.
11. <http://www.edwards.com/de/newsroom/Pages/ShowPR.aspx?PageGuid=%7B907fd876-d3f7-4aca-bbc9-6c4832d62197%7D>.
12. Box GEPCDR. An analysis of transformations. *J R Stat Soc Ser B (Methodological)* 1964; 26:211–252; 1964.
13. Monge Garcia MI, Pinsky MR, Cecconi M. Predicting vasopressor needs using dynamic parameters. *Intensive care medicine*. 2017.

16. APPENDIX I: DIAGNOSTIC GUIDANCE OF HYPOTENSION



17. APPENDIX II: SECONDARY SCREEN



Screenshot secondary screen. In the above picture the change of hypotension to occur is around 77%. The further parameters provide information on the possible underlying cause of the to occur hypotension. (10)

The secondary screen provides parameters to enable the anaesthetist to 'diagnose' the underlying cause of the predicted hypotension to choose the right treatment option (fluids, vasopressor or inotropes). The secondary screen divides the causes in a preload, contractility or afterload problem.

Explanation of the variables:

MAP= mean arterial pressure

Average systemic arterial blood pressure.

CO= cardiac output

Volume of blood ejected per minute from the heart into the systemic circulation measured in liters per minute.

PR=pulse rate= heart rate

SV = stroke volume

Amount of blood ejected from the ventricles with each contraction.

SVV=stroke volume variation.

Stroke volume variation is the percent difference between maximum and minimum stroke volume. A SVV>12% means the patient is fluid responsive. Fluid responsiveness means the cardiac output will increase when fluids are administered.

SVR=Systemic vascular resistance

A derived measure of impedance to blood flow from left ventricle (afterload).

Formula:

$$SVR = (MAP - CVP) \times 80 / CO \text{ (dyne-sec/cm}^5\text{)}$$

where: CVP - Central Venous Pressure

Dp/dt = a measure of left ventricular contractility from an arterial pressure waveform, for contractility. It is the maximal first derivative with respect to time of arterial pressure waveform

Formula:

$$dP/dt = \max(P[n+1]-P[n]), \text{ for } n=0 \text{ to } N-1$$

where:

P[n] - current sample of the arterial pressure signal, mmHg

N - total number of samples in a given cardiac cycle

Eadyn= Dynamic elastance

Dynamic arterial elastance is the ratio of pulse pressure variation and stroke volume variation (PPV/SVV). It is an estimate of arterial elastance. (13)

18. APPENDIX III: DIAGNOSTIC GUIDANCE OF HYPOTENSION deviations

Definition protocol deviation
1. HPI > 85% but no treatment started within 2 minutes
or
2. HPI >85% and treatment started however not the appropriate treatment started according to the study protocol suggestions
or
3. HPI>85% initially treatment started according to study protocol however on a later moment in time deviating from the protocol

For all protocol deviations will be noted:
<ol style="list-style-type: none"> 1. Reason protocol deviation motivated by treating Anaesthetist <ol style="list-style-type: none"> a. Clinical judgement b. Treatment option mentioned in the protocol not available in the OR c. Not aware of study d. Not motivated, because of intrinsic reasons, to stick to the study protocol 2. The researcher will discuss each protocol deviation and classify it as 'justly deviated from the protocol' versus 'unfairly deviated from the protocol'.
<p>For the study participants in the AMC this discussion will be performed by Denise Veelo, Marije Wijnberge and Bart Geerts.</p>