

**The Role of Acumen Hypotension Prediction Index Software
in Hypotension Management during Moderate to High-Risk
Non-cardiac Surgery: A randomized control trial**

Departments of General Anesthesiology

and OUTCOMES RESEARCH

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Study Title: The Role of Acumen Hypotension Prediction Index Software in Hypotension Management During Moderate to High-Risk Noncardiac Surgery: A pilot randomized control trial

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TRIAL SUMMARY

Design: Single-center randomized comparison of invasive arterial pressure monitoring vs. arterial pressure monitoring combined with Acumen Hypotension Prediction Index (HPI) software guidance on intraoperative hypotension duration and severity.

Anticipated enrollment period: 12 months

Aim: To determine whether use of Acumen HPI software guidance to guide intraoperative hemodynamic management in the non-cardiac surgery reduces the duration and severity of hypotension.

Primary hypothesis: Our primary hypothesis is that adding Acumen HPI software guidance to the information provided by the invasive arterial pressure monitoring during moderate- to high-risk noncardiac surgery reduces time-weighted average (TWA) intraoperative hypotension below a threshold of 65 mmHg.

Outcomes:

Primary

1. Time-weighted average MAP below a threshold of 65 mmHg per case.

Secondary

1. Time-weighted average MAP below a threshold of 60 mmHg per case;
2. Time-weighted average MAP below a threshold of 55 mmHg per case.

Exploratory

1. A collapsed composite of non-fatal cardiac arrest, in-hospital death, stroke, and MINS;
2. Acute kidney injury (AKIN criteria);
3. Quality of recovery (QoR-15) on postoperative day 3;
4. Postoperative morbidity survey (POMS) on postoperative day 3;
5. Transfusion requirement (ml packed red blood cells);
6. Amounts of intraoperative crystalloid and colloid;
7. Amount of vasopressors – phenylephrine, ephedrine, nor-epinephrine, epinephrine, dobutamine;
8. Advanced hemodynamic variables- Cardiac output (CO), Cardiac Index (CI), Stroke Volume (SV), Stroke Volume Variation (SVV);
9. Hospital length of stay;
10. Hospital readmission within 30 days.

Sample size: 213.

INTRODUCTION

In 2012, the global volume of surgery was estimated to be 312 million operations, a 33% increase from 2004.¹ According to Weiser et al, the increase in surgical volume is projected to grow with economic development. Surgery is associated with high mortality and morbidity, despite substantial improvements in technical expertise and patient monitoring. Overall inpatient 30-day mortality is about 2%, and climbs up to 6% in high-risk populations.²⁻⁷ More than 1% of patients aged 45 years or more die after major non-cardiac surgery while in the hospital or within 30 days of surgery.⁸

Cardiovascular events such as myocardial infarction (MI) and myocardial injury after non-cardiac surgery (MINS) are strongly associated with 30-day mortality.⁶ MINS is defined as myocardial injury caused by ischemia that occurs during or within 30 days after surgery. Elevated high-sensitivity troponin T measurement, diagnostic of MINS, is significantly associated with an increased risk of 30-day mortality (0.5% for <20 ng/L, 3.0% for 20 to <65 ng/L, 9.1% for 65 to <1000 ng/L, and 29.6% for ≥ 1000 ng/L).⁸ Without perioperative troponin monitoring, 93% of MINS and 68% of myocardial infarctions goes unrecognized because these patients do not experience ischemic symptoms.⁸ Many factors are strongly associated with MINS/MI, but most are unmodifiable baseline characteristics. But intraoperative hypotension is a distinctly modifiable factor which reduces the myocardial oxygen supply-demand ratio.

Intraoperative hypotension

Intraoperative hypotension is strongly associated with adverse outcomes.⁹⁻¹² In addition to being associated with MI, hypotension is implicated in the genesis of perioperative acute kidney injury and stroke.¹³ Recently Green et al demonstrated that 60% of surgical patients experience post-intubation hypotension, and that hypotension after induction of anesthesia is association with prolonged postoperative mechanical ventilation ICU length of stay.¹⁴ Overall, the incidence of intraoperative hypotension is surprisingly high and, depending upon the definition, ranges from 5 to 99%.¹⁵

Hypotension can be defined by absolute or relative criteria. Commonly used absolute thresholds for definition include systolic blood pressure (SBP) less than 90 mmHg or mean arterial pressure (MAP) less than 65 mmHg. Relative thresholds for describing hypotension include a 20% decrease in baseline SBP or a 30% decrease in MAP. Variability in definitions of intraoperative hypotension results because it remains unclear what thresholds are actually associated with harm. However, recent work has much enhanced our understanding of the relationship between intraoperative hypotension and adverse outcomes.

For example, in a retrospective cohort analysis (N=57,315), Salmasi et al reported that MAP below absolute thresholds of 65 mmHg and lower or relative thresholds of 20% or more below baseline were progressively related to both myocardial and kidney injury (Figure 1). The investigators also found that the associations based on relative thresholds were no stronger than those based on absolute thresholds — which are easier to use.

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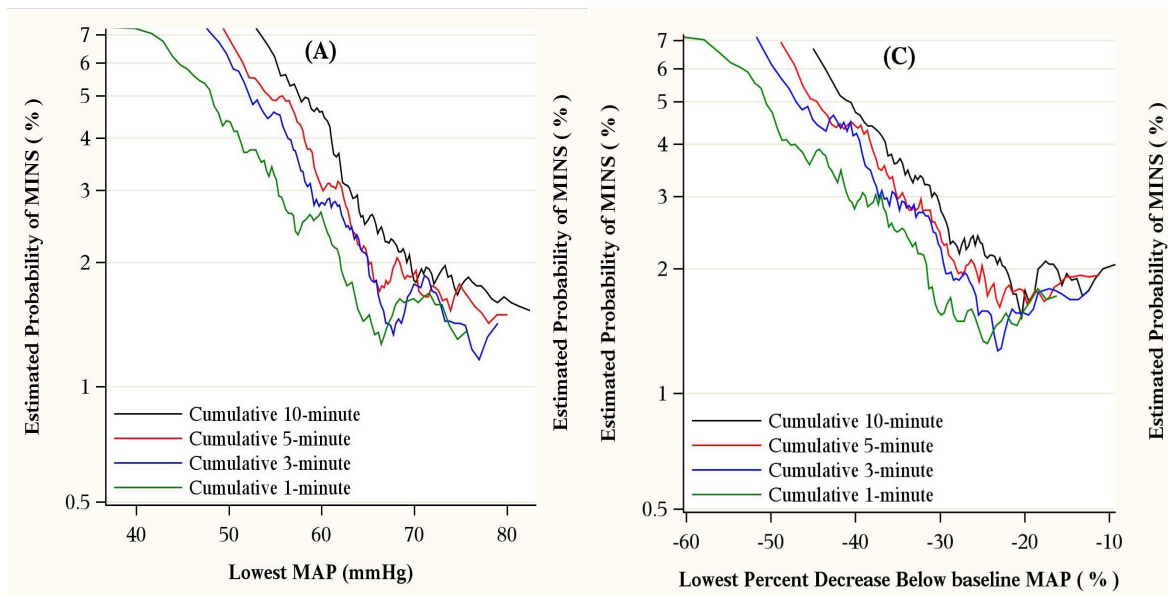


Figure 1 – A 20% reduction from baseline worsens myocardial injury & mortality — but is not a better than absolute threshold of MAP <65 mmHg. Salmasi et al¹³

Anesthesiologists are primarily responsible for intra-operative blood pressure management. Given the strong associations between hypotension and myocardial injury, acute kidney injury, and death, it seems likely that harm can be ameliorated by timely and appropriate intervention by anesthesiologists to decrease the amount of intraoperative hypotension. However it is difficult to predict and prevent intraoperative hypotension. Recently Cheung et al developed the HEART score to predict intraoperative hypotension or bradycardia intra-operatively.¹⁶ However, the Prediction is on a per-patient basis, and does not provide minute-by-minute guidance for intraoperative management. Furthermore, the score has not been externally validated and was derived from a small cohort.

Acumen Hypotension Prediction Index

The Acumen Hypotension Prediction Index (HPI) software suite is enabled by the minimally invasive FloTrac IQ sensor.¹⁷⁻¹⁹ The FloTrac IQ sensor is the hardware which is connected to the existing arterial catheter. The hemodynamic information is presented on Edwards EV1000 platform. Thus whole system is comprised of

- **FloTrac IQ sensor (hardware):** FloTrac IQ is the sensor (Figure 2a) which is connected to the standard arterial catheter tubing from the patient. The sensor then relay information to the standard anesthesia monitor in the form of continuous arterial pressure waveform. The sensor also relay information to Acumen HPI enabled EV1000 platform.
- **Acumen HPI (software) :** The software unlocks the Hypotension Prediction Indicator and other advanced hemodynamic parameters (Appendix 1)
- **EV1000 (screen platform):** This is the platform (Figure-2b). which displays the continuous arterial pressure monitoring, HPI and the advanced hemodynamic parameters.

The hemodynamic information includes following three elements:

- (1) A continuous arterial pressure waveform including blood pressure readings. This arterial waveform is also shown on the standard anesthesia monitor.
- (2) The hypotension Prediction parameter, which indicates the possibility of a hypotensive event using machine learning techniques developed from more than 20,000 past patient events. The HPI (0-100%) gives a percent Prediction of hypotension in coming minutes. For example, a HPI of 85 indicates that there is roughly an 85% chance of hypotension to occur in the subsequent five minutes (Table 1). An alarm (audible and visual) is incorporated in the system that alerts clinicians when hypotension Prediction exceeds an upper threshold.
- (3) Advanced hemodynamic parameters are displayed a secondary screen (Figure 2) which provide information on the pathophysiology of the predicted hypotension. The traditional explanation of hypotension pathophysiology is based on three distinct concepts - preload, afterload and contractility. And based on these concepts the treatment of hypotension can consist of - fluids, vasopressor and/or inotropes (Figure 3). The advanced hemodynamic variables (Appendix -1) 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) can aid clinicians in the diagnosis, treatment and evaluating the treatment response.²⁰ All parameters are described in the Appendix 1.

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Figure 2a – FloTrac IQ sensor

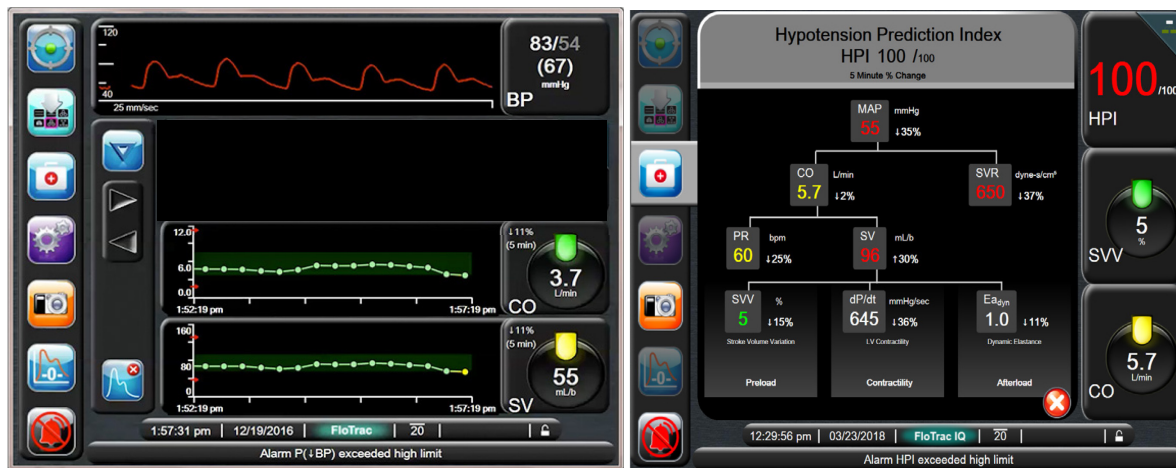


Figure 2b – EV 1000 platform primary and secondary screen . In the above screenshot the HPI is 71% and the advanced hemodynamic parameters cardiac output (CO), stroke volume (SV), stroke volume variation (SVV), rate of contractility (dP/dt), dynamic elastance ($E_{a_{dyn}}$) are shown.

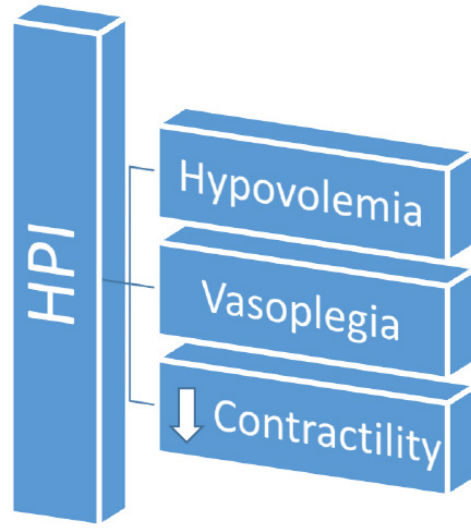


Figure 3 – Pathophysiology of hypotension.

Animal studies

The performance of the HPI was assessed in a porcine model (unpublished 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 60 mmHg and sustained for 15 min and fluid resuscitated via auto transfusion to MAP of 85 mm/hg for 30 min. Then hypotension was induced by infusion of nitroprusside to reduce MAP less than 65 mmHg for 15 min.

The two models create hypotension in distinct modalities.

- The hemorrhage model directly reduces blood volume, demonstrating the direct relationship between hypotension prediction 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 Prediction indicator (HPI), heart rate (HR), stroke volume variation (SVV), dP/dt , arterial dynamic elastance (E_{adyn}), stroke volume (SV), systemic vascular resistance (SVR), end-diastolic volume index (EDVI), and ejection fraction (EF) were measured. (Figure 4) 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 E_{dyn} 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 prediction 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.

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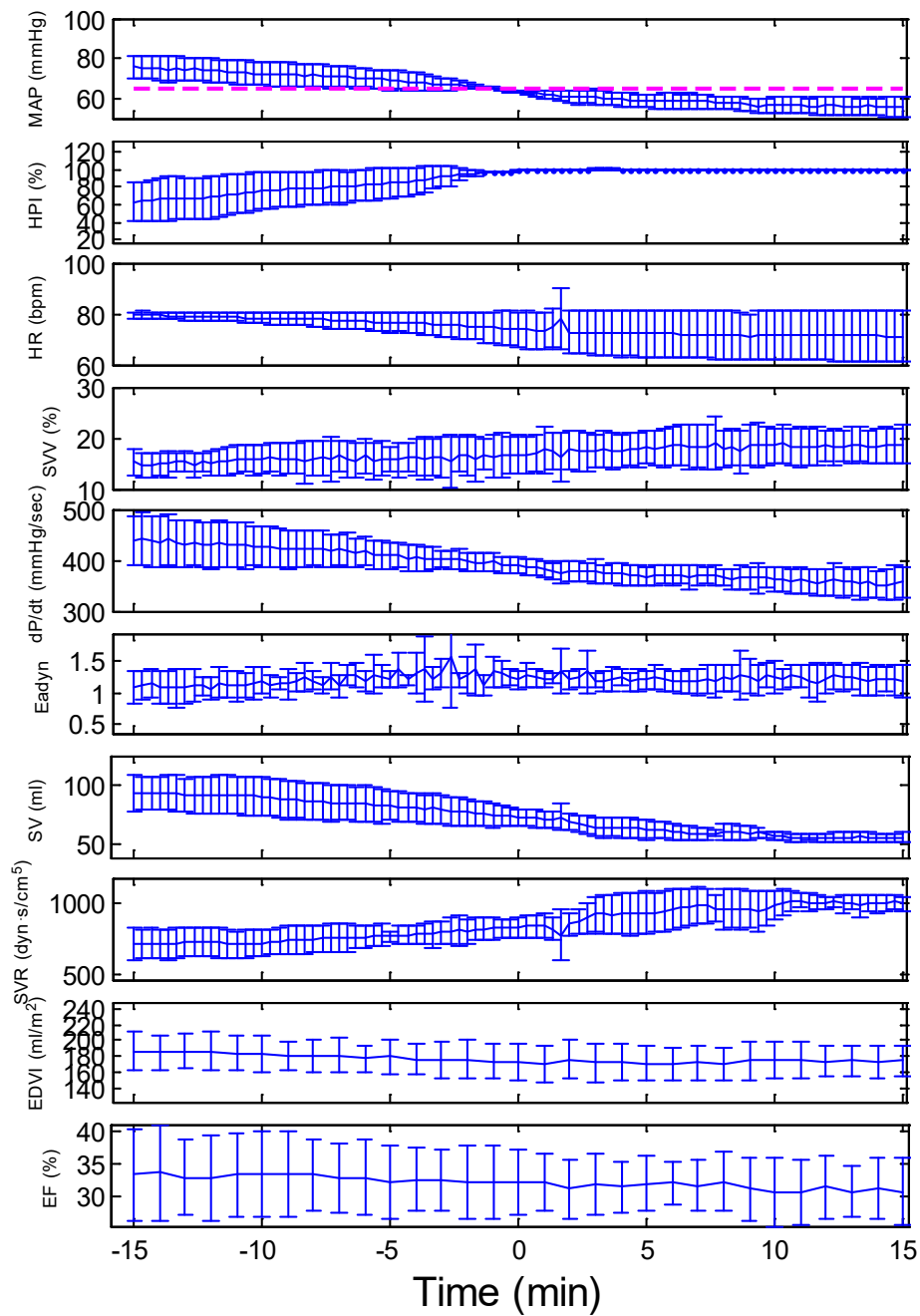


Figure 4: mean \pm SD vital signs and hemodynamic parameters in the hemorrhage model for all animals before and after 15 minutes of hypotension. Time 0 is the time when hypotension happens. From top to bottom: mean arterial pressure (MAP), hypotension Prediction indicator (HPI), heart rate (HR), stroke 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.

Clinical studies

The HPI was developed on an offline clinical dataset of 293 patients including 97 in operating rooms and 196 in critical care units. 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 modelling 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.²¹ 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%, 5min, 10 mins and 15 mins prior to the event respectively.(Figure 5) The software is CE marked and already on the European market available for use in humans. The FDA has reviewed and granted de novo request DEN160044; a reclassification order allowing the software to be marketed in the US

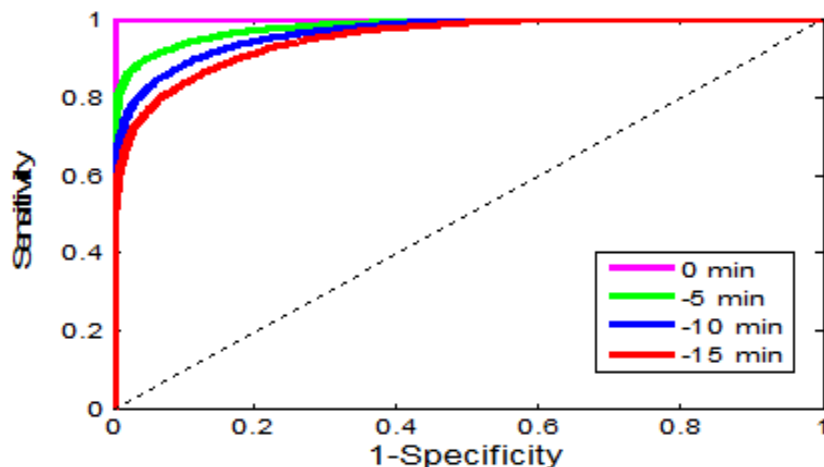


Figure 5: Reliability of the hypotension Prediction indicator (HPI) to predict a hypotensive event in time prior to the event. *Veelo et al, ASA conference, 2016*²¹

STUDY RATIONALE

Even when clinicians try to prevent intraoperative hypotension, they often fail because it is difficult to predict which patients will become hypotensive, much less when. A risk score for predicting minute-by-minute intraoperative hypotension is not currently available. Yet it seems likely that ability to identify when a patient is likely to become hypotensive, and the pathophysiology of the event, will improve hemodynamic management and perhaps patient outcome. Acumen HPI appears to be a reliable predictor of intraoperative hypotension, and should thus help clinicians anticipate and avoid hypotension. Furthermore, the secondary guidance provided by the Acumen HPI may help clinicians optimally manage fluids and thus prevent future episodes in the same patient.

AIMS

To determine whether use of Acumen HPI software to guide intraoperative hemodynamic management in the non-cardiac surgery reduces the duration and severity of hypotension.

PRIMARY HYPOTHESIS

Our primary hypothesis is that use of the Acumen HPI software guidance reduces TWA intraoperative hypotension below a threshold of 65 mmHg.

Specifically, we will compare the amount of intraoperative hypotension below mean-arterial pressure (MAP) threshold of 65 mmHg, in patients randomized to invasive arterial pressure monitoring vs. invasive arterial pressure monitoring with Acumen Hypotension Prediction Index software.

OUTCOMES

Primary:

1. Time- weighted average (TWA) MAP under a threshold of 65 mmHg.

Secondary:

1. Time-weighted average MAP below a threshold of 60 mmHg per case;
2. Time-weighted average MAP below a threshold of 55 mmHg per case.

Exploratory:

1. A composite of non-fatal cardiac arrest, in-hospital death, stroke, and MINS;
2. Acute kidney injury (AKIN criteria);
3. Quality of recovery (QoR-15) on postoperative day 3;
4. Postoperative morbidity survey (POMS) on postoperative day 3;
5. Transfusion requirement (ml packed red blood cells);
6. Amounts of intraoperative crystalloid and colloid;
7. Amount of vasoactive – phenylephrine, ephedrine, nor-epinephrine, epinephrine, dobutamine;

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8. Advanced hemodynamic variables- Cardiac output (CO), Cardiac Index (CI), Stroke Volume (SV), Stroke Volume Variation (SVV), Dynamic elastance (Edyn);
9. Hospital length of stay;
10. Hospital readmission within 30 days.

	Outcomes	Measurements
1. Primary	TWA MAP drop under 65 mmHg threshold	Intraoperative record form EV1000 monitor
2. Secondary	TWA MAP drop under 60 mmHg threshold	Intraoperative record form EV1000 monitor
	TWA MAP drop under 55 mmHg threshold	Intraoperative record form EV1000 monitor
3. Exploratory	Composite of death, stroke, or MINS	From Cleveland Clinic Perioperative Health Documentation System PHDS and troponin first three postoperative mornings while in hospital from electronic health record (EHR)
	Acute kidney injury	AKIN, creatinine
	Quality of recovery (QoR-15):	POD 3 , patient interview
	Post-operative morbidity survey (POMS)	POD 3 , EHR
	Transfusion requirements (ml)	from PHDS
	Amounts of intraoperative crystalloid and colloid (ml)	from PHDS
	Amount of vasoactive – phenylephrine, ephedrine, nor-epinephrine, epinephrine, dobutamine (mg)	from PHDS

	Advanced hemodynamic variables	From EV100
	Hospital length of stay	From PHDS
	Hospital readmission within 30 days	From EHR

STUDY DESIGN

Experimental design

Single-center randomized comparison of invasive arterial pressure guided hypotension management vs. addition of Acumen HPI software guidance to the invasive arterial pressure monitoring on intraoperative hypotension duration and severity.

Subject selection

We will enroll ASA physical status 3-4 patients scheduled for moderate-to-high-risk surgery, who are ≥ 45 years of age. Potentially qualifying patients will be evaluated during their preoperative anesthesia clinic visits. We will enroll surgical patients meeting the following criteria:

Inclusion criteria

1. Written informed consent;
2. Age ≥ 45 years;
3. ASA Physical Status 3 or 4;
4. Moderate- or high-risk surgery (for example, orthopedic, spine, urology, and general surgery);
5. Planned invasive blood pressure monitoring;
6. General anesthesia;
7. Surgery duration expected to last > 2 hours;
8. Planned overnight hospitalization.

Exclusion criteria

1. Contraindication to the invasive blood pressure monitoring;
2. Pregnancy;
3. Emergency surgery;
4. Known clinically important intracardiac shunts;
5. Known aortic stenosis with valve area ≤ 1.5 cm²
6. Known moderate to severe aortic regurgitation
7. Known moderate to severe mitral regurgitation
8. Known moderate to severe mitral stenosis

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9. Patient or surgical procedure type known as an SVV limitation¹⁶ (e.g. tidal volume <8mL/kg of theoretical ideal weight, spontaneous ventilation, persistent cardiac arrhythmia, known atrial fibrillation, open chest surgery, Heart Rate/Respiratory Rate (HR/RR) ratio <3.6)
10. Current persistent atrial fibrillation
11. Congestive heart failure with ejection fraction <35%
12. Neurosurgery
13. Emergent or cardiovascular surgical procedure
14. Patient who is confirmed to be pregnant
15. Refusal of patient or authorized representative to sign consent

Patients will be recruited from the Operating Room schedule. Written, informed consent will be obtained from each subject. All participants will be specifically informed that they may decline to participate in, or withdraw from, the study at any time

Protocol

Anesthetic care will be per clinical routine. There is no restriction on type of general anesthesia, and regional anesthesia/analgesia is permitted.

In addition to the standard ASA monitors, all patients will have an arterial catheter inserted for pressure monitoring. The catheter will be connected to a FloTrac IQ sensor and to EV1000 platform which includes Acumen HPI software.

Shortly before induction of anesthesia, patients will be randomly assigned to one of two groups using a reproducible set of computer-generated random numbers. We will use web-based, computer-generated randomization, prepared by our biostatistician, and accessed shortly before induction of anesthesia to conceal allocation to the extent practical. Patients will not be informed of their group assignments.

The randomized groups will be:

- 1) Access to arterial waveform and pressures from the standard anesthesia monitor.
- 2) Access to arterial waveform and pressures from the standard anesthesia monitor and information from an Acumen HPI-enabled EV1000 screen.

The amount and timing of intravenous fluids and vasopressor drugs will be decided by the anesthesia team based on the guidance from the software in the intervention group. The software provide multiple parameters. In order to standardize the interpretation of hemodynamic parameters clinicians at Cleveland Clinic has agreed to the conceptual framework presented in Figure 6. In the arterial pressure monitoring group without Acumen HPI, clinicians will make treatment decision based on the pressure waveform. In all cases, good clinical judgment will be predominant, and the attending anesthesiologist take all necessary steps to provide optimal and safe care. Blood and blood products will be administered based on clinical judgment.

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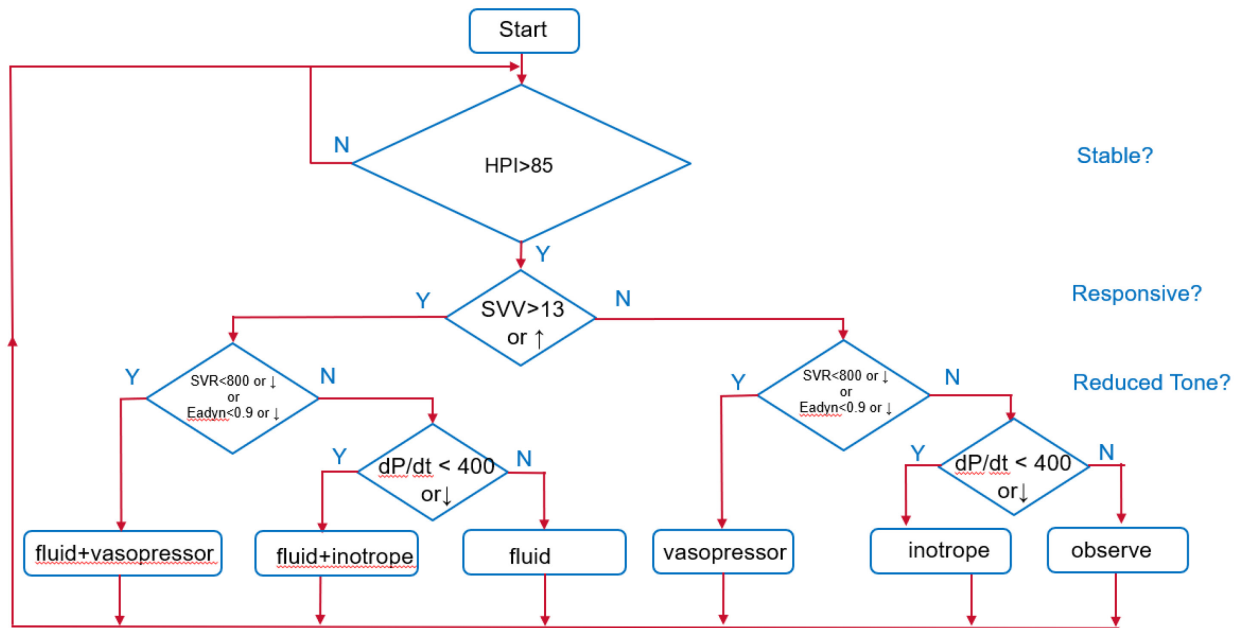


Figure-6 Conceptual framework for the hemodynamic management

A research fellow will be present in the operating room and will monitor the HPI value and the response by the clinical team every 15 min and also when HPI >85. He will specifically document the HPI number and the hemodynamic state – hypovolemia, vasoplegia and decreased contractility and document the clinician's response as following

Table 1- Intraoperative data collection

Time stamp	HPI value	Hemodynamic state per clinical team	Hemodynamic state per Acumen HPI
1.			
2.			
3.			
4.			
5.			

Blinding

Patients will be blinded to group allocation. Anesthesiologist, surgeons, data gathering research personnel and operating room team cannot be blinded to the treatment arm. Principal investigators, co-investigators and the data analysis team will be blinded for the treatment groups. The amount and timing of intravenous fluids and vasopressors will be decided by the anesthesia team based on the clinical assessment which is current standard of care.

Postoperative Management

The attending anesthesiologists and surgeons, taking into account the clinical condition of individual patients and risk of complications, will determine whether postoperative ICU admission is appropriate.

Measurements

Baseline Information: We will record demographic and morphometric characteristics include height (cm), weight (kg), age (yr.), sex, ASA physical status, and self-declared ethnicity. If available we will collect social history (tobacco and alcohol use), medical history (pulmonary disease, cardiovascular disease, neurologic disease, drug usage (including but not limited to: statins, β blockers, oral hypoglycemic agents and/or insulin), NSAIDs, diabetes (and whether insulin-dependent or not), and previous glucose-tolerance test results, preoperative hemoglobin and hematocrit, BUN and creatinine, electrolytes, preoperative EKG, and hemoglobin A_{1c} (HbA_{1c}). We will obtain contact information for each patient to facilitate follow-up.

Perioperative Data: Intraoperative care data will be accessed from electronic anesthesia information management system. The hemodynamic monitoring data will be downloaded from the monitors on to the secure Cleveland Clinic computers for analysis.

Anesthetic data will include the volatile anesthetic dose in MAC-hours, as well as total doses of propofol and other sedative hypnotics. Hemodynamic, respiratory parameters, BIS values and esophageal temperature will be recorded at regular intervals intraoperatively. Blood loss will be estimated; urine output and fluid administration including allergenic blood will be recorded. Intraoperative use and total dose of vasoactive drugs as well as antibiotic administration will be recorded. If available arterial blood gas results will be recorded.

Blood pressure measurements: A research fellow will be present in the operating room throughout the surgery. The research fellow will document when HPI alerts were generated and what is the probable cause based on the advanced hemodynamic parameters – hypovolemia, vasoplegia or decreased left ventricular contractility. The research fellow will also document the clinician's response; no action, fluid bolus, vasopressor started or increased, and inotrope started or increased. The hemodynamic monitoring data will be downloaded from the monitors on to the secure Cleveland Clinic computers for analysis.

Length of stay: Length of stay (LOS) will be calculated end of surgery to time of discharge or death. We are considering Hospital LOS because not only it reflects morbidity, but also is important from hospital administration point of view, because hospitals want to utilize their resources in the most cost-effective way. According to Agency for Healthcare research and Quality average in 2010,

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average hospital cost per stay was \$9,700, totaling \$375.9 billion.²² Furthermore, recent consideration of bundled payments by payers to reduce cost of healthcare while providing highest quality healthcare has provided increased impetus by the hospitals for reducing hospital LOS.

Table 2- Schedule of study events

Data	Screening Evaluation	Enrollment	Hemodynamic monitoring	Postoperative day three
Informed Consent	x			
Inclusion/Exclusion Criteria Evaluation	x			
Medical History		x		
Demographic		x		
Vital Signs		x	x	
Surgery Information		x		
Monitoring duration			x	
Device memory data			x	
Adverse events			x	x
Hemodynamic management information			x	
Intraoperative medications			x	
Quality of recovery				x

Follow up

Patient will be followed up for major and minor complications as listed above. Patients will have a Troponin T drawn preoperatively and on the first and second days after surgery while patients remain hospitalized. Study personnel will recommend and attempt to obtain an ECG and/or

echocardiogram on patients with an elevated Troponin T. Patients will be queried about ischemic symptoms and pulmonary edema.

Research personnel will follow patients throughout their time in hospital evaluating the patients and reviewing their medical records ensuring trial orders are followed and noting any outcomes. If records/ patients indicate that they have experienced an outcome, study personnel will obtain the appropriate documentation.

PATIENT RECRUITMENT AND INFORMED CONSENT

To ensure efficient recruitment, research personnel will screen the patient list in the preoperative assessment clinic to identify eligible patients. Research personnel will use a variety of screening approaches to capture patients who do not attend the preoperative assessment clinic, including screening: the daily surgical list in the operating room, patients on surgical wards and intensive care units, and patients in the preoperative holding area. Center will also use all potential patient sources including asking the services of anesthesia, surgery, and medicine to page the study personnel regarding all surgical admissions through the emergency department and consultations for floor patients requiring surgery. Research personnel will approach all eligible patients to obtain informed consent. We will enroll patients undergoing surgery at single institution (Cleveland Clinic foundation, Cleveland, Ohio, USA)

DATA ANALYSES

Randomized groups will be compared on baseline variables using the standardized difference (difference in means or proportions divided by the pooled standard deviation), and such variables will be considered balanced if the absolute standardized difference is $< 1.96 \sqrt{2/N}$, where N is the per group sample size. Imbalanced variables will be adjusted for in all analyses.

The treatment effect of Acumen HPI guidance (versus no Acumen HPI guidance) on the primary outcome of intraoperative time- weighted average (TWA) MAP under a threshold of 65 mmHg will be assessed with a Wilcoxon-Mann-Whitney 2-sample 2-tailed test, or analogous test to account for imbalanced baseline variables or non-normal distribution of the outcome, as needed. Secondary and exploratory continuous outcomes will be analyzed in the same way.

Randomized groups will be compared on binary outcomes using a Pearson chi-square test or else logistic regression to adjust for baseline variables, as needed, and on oral outcomes using either the Wilcoxon Mann-Whitney test or a proportional odds logistic regression model, as appropriate.

For all analyses, focus will be on the estimated treatment effects and their confidence intervals, as well as the P-values. SAS statistical software, Carey, NC, will be used for all analyses.

SAMPLE SIZE CONSIDERATIONS

Summary. From our a-line study [unpublished] we observed mean (SD) of area under the curve AUC-MAP<65 of 80 (127) and median [quartiles] of 24 [1, 121]. Similar to time weighted average AUC-MAP represents depth and duration of hypotension. $\text{AUC-MAP} = \text{TWA-MAP} \times \text{duration of observation}$. The data is highly skewed, with a non-trivial proportion of zeros. Therefore, it is not appropriate to base a sample size estimate on a t-test which assumes normality. It is best based on a non-parametric test such as the Wilcoxon-Mann-Whitney test, as put forth in the preliminary protocol for the larger study. In that study we needed about 800 patients to detect a 50% reduction in the median, based on 90% power and incorporating interim analyses. For the calculations below we use 80% power. As noted below, for the current study we recommend a total sample size of 213 to detect an approximate 20% reduction in the mean of the primary outcome of $\text{AUC-MAP} < 65 \text{ mmHg} \times \text{min}$, which based on the pilot data corresponds to a Wilcoxon-Mann-Whitney probability (i.e., a c-statistic) of 0.61.

Detailed calculations. In the below Table 3, using the same calculations based on the Wilcoxon-Mann-Whitney test as in the proposal for the larger HPI trial, we present the required sample size to detect reductions or shifts in the distribution of the primary outcome ($\text{AUC-MAP} < 65 \text{ mmHg} \times \text{min}$) which are equal to various percentages (*achieved* reductions ranging from 7% to 35%) of the control group mean. The reduction is applied on a case level (i.e., for each control observation), so that a reduction of say 10% of the mean would reduce all observations by 8 mm Hg x min (0.10 x control group mean (80 mmHg x min)). But if that brings an observation below zero, the value of zero is used (cannot have negative AUC!). Table 3 thus gives a top row for the *attempted* reduction (on the case level), and then the *achieved* HPI mean and median, as well as the ratio (HPI/control) of means and medians.

Recommended Sample Size of total N=213: In the 35% attempted reduction column, a reduction of 35% of the control mean (equal to 28 mmHg x min) was *attempted* for all control cases when constructing the HPI distribution of outcomes. The *achieved* ratio of means was 0.79, indicating a 21% reduction in the mean. The achieved reduction was not the full 35% since, as expected, many of the cases reached zero instead of the full attempted reduction. This scenario also brought the HPI median (and thus the ratio of medians) to zero. The scenario requires a total of 213 patients (107 / group). The Wilcoxon-Mann-Whitney probability of 0.61 means the probability that randomly chosen HPI patient has lower AUC-MAP<65 compared to random control patient is 0.61.

Table 3: Sample size to detect various reductions in AUC-MAP<65 for HPI vs control Recommended sample size in the 35% attempted reduction column is total N=213								
Assume control group median [q1,q3] = 24 [1, 121]; mean (SD) =80 (127); zeros = 27% Power=80%, alpha=0.05, no interim analyses								
<i>Attempted Reduction*:</i> % of control mean (mmHg x min)	10% (8)	20% (16)	30% (24)	35% (28)	40% (32)	50% (40)	60% (48)	70% (56)
<i>Achieved reduction</i>								
HPI group Median	16	8	0.5	0	0	0	0	0
Ratio of medians	.67	.33	.02	0	0	0	0	0
HPI group mean	75	70	66	64	62	58	55	51
Ratio of means	.93	.87	.81	.79	.77	.72	.68	.64
Total N	1511	460	261	213	187	140	115	93
WMW prob (P')	.54	.57	.60	.61	.62	.63	.65	.67
1/ WMW odds	.85	.74	.67	.64	.62	.58	.54	.50
<p>*Attempted Reduction: Amount of attempted reduction in AUC-MAP<65 for each observation, listed as percent of control MEAN and in actual units. Achieved individual reduction was less (or even zero) in some cases since true value for an individual cannot go below zero.</p> <p>HPI median: median of HPI group after the induced shift Ratio of medians: HPI median / control median (24 mmHg x min)</p> <p>HPI mean: mean of HPI group after the induced shift Ratio of means: HPI mean / control mean (80 mmHg x min)</p> <p>WMW prob (P'): Wilcoxon-Mann-Whitney probability (P'). Equal to a c-statistic from logistic regression. Probability that randomly chosen HPI patient has lower AUC-MAP<65 compared to random control patient. P' = 0.50 under null hypothesis (i.e., would be achieved by guessing), and 1.0 is perfect discrimination.</p>								

1/WMW odds: Odds of having a lower value of AUC-MAP<65 in HPI vs control group. Equal to $1 / (P'/(1-P'))$. Equals 1 under null hypothesis. Values < 1 indicate increasingly stronger effect.

DATA MANGEMENT AND QUALITY ASSURANCE

Executive committee

An executive committee comprised of the principal investigator, Drs. Sessler and Kurz, and Dr. Edward J. Mascha (lead statistician) will oversee the data management and quality assurance. The executive committee will also review the conduct of the study; and help identify and resolve problems with recruitment or performance.

Data management

Procedures used to assure the integrity of data include (1) quarterly external audits by **OUTCOMES RESEARCH** staff, (2) data entry procedures following standard operating procedures (SOPs), and (3) data queries and resolution processes following SOPs. Frequent interaction among members of the study Executive Committee (PI, co-investigators), and others as necessary, will maintain overall quality assurance. They will meet or have conference calls at least quarterly throughout the data collection period, and as necessary thereafter.

A standard form for data collection will be used. The key variables for intraoperative management and postoperative data collection are explicitly defined in the data form. Qualified and trained individual will enter the information into research database, to decrease the variability and to ensure quality of essential data. Hard-copy forms will be stored in locked cabinets within a secured area. To protect electronic records and files against loss, duplicate files will be maintained on the Anesthesiology Institute servers at the Cleveland Clinic. These servers are highly secured because they already contain much patient-related information and are backed up daily to tape that is maintained in a remote location. The system fully meets all applicable HIPAA Privacy and Security rules. Access to the database and backups are strictly monitored according to need.

An initial training meeting before study enrollment will ensure reliability and consistency in the use of Acumen HPI software and written standard operating procedures (SOPs). At least 80% of the data will be independently audited to confirm consistency among patient records, study data sheets, and the main database. Data will be maintained on a custom-designed Access or SQL relational database. Data will be transcribed by separate sets of investigators. We have programmed and used similar password-protected databases in our previous major outcome trials. Trial management will be coordinated from the department of Outcomes Research, Cleveland.

HUMAN SUBJECTS RISKS AND PROTECTION

The Cleveland Clinic Institutional Review Board will approve the proposed trial. Written informed consent will be obtained from each participating patient. Patients who decline to participate will be given regional or general anesthesia and analgesia per their preference and that of their attending anesthesiologist; research data will not be collected from these patients.

1. Human Subjects Involvement and Characteristics:

The executive committee which will not otherwise be involved in day-to-day aspects of the protocol, will evaluate all results from the proposed trial. This committee, along with the IRB, will have exclusive authority to stop the studies either because the hypotheses have been confirmed, denied, or because adverse events are detected. It will be the responsibility of this committee to alert the IRB at each participating institution to any untoward toxicity in one of the study groups.

2. Sources of Material

Data obtained routinely for clinical purposes will be used in this study. Such data include: 1) anesthetic dose and safety monitoring; 2) fluid balance and transfusion requirements; 3) postoperative nausea and vomiting; 4) details of surgery; and 5) morphometric and demographic information. Postoperative outcomes will be retrieved daily from the patients' charts.

3. Potential risks to Subjects

Monitoring and Data Collection: Some data obtained routinely for clinical purposes will be used in this study. Such data include: anesthetic concentration and safety monitoring (end-tidal gases, arterial blood pressures, oxygen saturation, esophageal temperatures, intraoperative arterial blood gas samples, etc.), fluid balance, and urine volume. Recording these data is clinical standard and introduces no additional risk.

Randomized treatments: Only patients needing arterial line placement for hemodynamic monitoring will be included. The information from the additional monitor Acumen HPI will be used in addition to the standard monitoring. Use of crystalloid LR is normal practice for perioperative fluid administration. Clinicians are not bound to any treatment recommendation and will use best clinical judgement at any time for patient care.

Acumen HPI Monitoring: HPI and other advanced hemodynamic parameters will be displayed on the monitor in the intervention arm. The software is CE marked and already on the European market available for use in humans. The FDA has reviewed and granted *de novo* request DEN160044; a reclassification order allowing the software to be marketed in the US

Patient Privacy: Patient privacy will be fully respected. The investigators will discuss with subjects and their assigned representatives, the IRB-approved informed consent explaining all procedures and potential risks, and the HIPAA regulations regarding privacy of their medical information. Participating patients will complete the appropriate HIPAA forms.

Access to medical records is limited to the investigative staff. Data will be managed by study number and analyzed anonymously. All reports will be of a summary nature and no individual will

be identified. The investigators and study coordinators are keenly aware of the increasing ethical concerns of using medical information in research and its potential misuse in clinical care. They will insure that data will be handled appropriately and that confidentiality is strictly maintained. All members of the study staff will sign agreements of confidentiality.

4. Recruitment and Informed Consent

Patients will be recruited from the Operating Room schedules. A specially trained member of the study staff will approach potential subjects at the Cleveland Clinic in the Preoperative Clinic or surgeon's office and give a general description of the study and its purpose to the patient. Patients who orally agree will be given the Informed Consent document and asked to read it carefully. If for some reason they cannot read it themselves, it will be read to them. Any questions will be fully answered. Once patients completely understand the procedure, benefits, and risks involved, they will be asked to sign and date the consent form.

Two copies of the Informed Consent form will be made. One copy remains in the patient's chart, another copy will be given to the patient, and the original will be filed with the case report form. The original consent will thus be available to the investigators, their staff, study monitors, and each institution's IRB.

5. Protection against Risks

All interviewers will undergo training by our consenting study coordinators and must demonstrate a high level of proficiency before being certified to interview subjects. Research fellows and study coordinators will be trained in all aspects of the study. Procedures used to assure the integrity of data include: (1) quarterly external audits by Outcomes Research staff, (2) data entry procedures following standard operating procedures (SOPs), and (3) data queries and resolution processes following SOPs. Frequent interaction among members of the study Executive Committee (PI, co-investigators, consultants), RAs, and others as necessary, will maintain overall quality assurance. They will meet or have conference calls at least quarterly throughout the data collection period, and as necessary thereafter.

The executive committee will evaluate all results from the proposed trial at least yearly, but more often if the Committee deems it necessary. It will be the responsibility of this committee to alert the IRB *via* letter to any untoward toxicity in one of the study groups. This committee, along with the IRB, will have exclusive authority to stop the study either because the hypotheses have been confirmed or denied, or because adverse events are detected. The executive committee will operate under guidelines published on the NCI web site.

6. Collaborating Sites

Single center

7. Gender and Minority Inclusion

We have no reason to believe that the effects of hemodynamic management on outcome are related to race or ethnicity. We will consequently include patients of all races and ethnicities and make a special effort to include minorities. We assume that our study population will reflect the patient

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population of each participating health system. In Cleveland, our participants will be roughly 10% Hispanic and 15% African American.

8. Inclusion of Children

Children will be excluded from the proposed studies.

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TABLES

Table-1 The distribution of the probabilities and the event rate. Proprietary data from humans

HPI (%)	Event Rate (%)	Time (min), Median, [10th, 90th 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]

APPENDIX

1. Description of hemodynamic parameters

- 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: $SVR = (MAP - CVP) \times 80 / CO$ (dyne-sec/cm⁵) 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: $dP/dt = \max(P[n+1]-P[n])$, for n=0 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

2. Quality of recovery questionnaire (QOR-15)

QoR-15 Patient Survey

Date: __/__/__

Study #: _____

Preoperative ☐

Postoperative ☐

PART A

How have you been feeling in the last 24 hours?

(0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

- | | | | | | | | | | | | | | |
|---|------------------|---|---|---|---|---|---|---|---|---|---|----|-----------------|
| 1. Able to breathe easily | None of the time | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | All of the time |
| 2. Been able to enjoy food | None of the time | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | All of the time |
| 3. Feeling rested | None of the time | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | All of the time |
| 4. Have had a good sleep | None of the time | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | All of the time |
| 5. Able to look after personal toilet and hygiene unaided | None of the time | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | All of the time |
| 6. Able to communicate with family or friends | None of the time | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | All of the time |
| 7. Getting support from hospital doctors and nurses | None of the time | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | All of the time |
| 8. Able to return to work or usual home activities | None of the time | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | All of the time |
| 9. Feeling comfortable and in control | None of the time | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | All of the time |
| 10. Having a feeling of general well-being | None of the time | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | All of the time |

PART B

Have you had any of the following in the last 24 hours?

(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

- | | | | | | | | | | | | | | |
|--------------------------------|------------------|----|---|---|---|---|---|---|---|---|---|---|-----------------|
| 11. Moderate pain | None of the time | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | 0 | All of the time |
| 12. Severe pain | None of the time | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | 0 | All of the time |
| 13. Nausea or vomiting | None of the time | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | 0 | All of the time |
| 14. Feeling worried or anxious | None of the time | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | 0 | All of the time |
| 15. Feeling sad or depressed | None of the time | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 | 0 | All of the time |

The quality of recovery score (QoR)-15 questionnaire.

3. The POMS (Grocott MP et al)

Morbidity type	Criteria	Source of data
Pulmonary	Has the patient developed a new requirement for oxygen or respiratory support.	Patient observation
		Treatment chart
Infectious	Currently on antibiotics and/or has had a temperature of >38°C in the last 24 hr.	Treatment chart
		Observation chart
Renal	Presence of oliguria <500 mL/24 hr; increased serum creatinine (>30% from preoperative level); urinary catheter in situ.	Fluid balance chart
		Biochemistry result
		Patient observation
Gastrointestinal	Unable to tolerate an enteral diet for any reason including nausea, vomiting, and abdominal distension (use of antiemetic).	Patient questioning
		Fluid balance chart
		Treatment chart
Cardiovascular	Diagnostic tests or therapy within the last 24 hr for any of the following: new myocardial infarction or ischemia, hypotension (requiring fluid therapy >200 mL/hr or pharmacological therapy), atrial or ventricular arrhythmias, cardiogenic pulmonary edema, thrombotic event (requiring anticoagulation).	Treatment chart
		Note review
Neurological		Note review

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Morbidity type	Criteria	Source of data
	New focal neurological deficit, confusion, delirium, or coma.	Patient questioning
Hematological	Requirement for any of the following within the last 24 hr: packed erythrocytes, platelets, fresh-frozen plasma, or cryoprecipitate.	Treatment chart
		Fluid balance chart
Wound	Wound dehiscence requiring surgical exploration or drainage of pus from the operation wound with or without isolation of organisms.	Note review
		Pathology result
Pain	New postoperative pain significant enough to require parenteral opioids or regional analgesia.	Treatment chart
		Patient questioning

4. Non-cardiac surgeries routinely requiring invasive monitoring:

Vascular surgeries: Bypasses for Peripheral Arterial Disease, Carotid Endarterectomy, AAA repair (open or endovascular)
Spinal surgeries: thoracolumbar fixations/instrumentation for scoliosis
Orthopedic procedures: Femoral fracture fixation
Head & Neck procedures: Laryngectomies, flap reconstructive surgeries
Thoracic Surgery: VATS, lobectomies, pneumonectomies, mediastinal tumor excision, Esophagectomy, Redo Nissen fundoplication
GI & Colorectal surgery: Total proctocolectomy, Whipple's procedure, laparoscopic adrenalectomies

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Genitourinary procedures: Cystectomies with creation of ileal conduit, Partial nephrectomies
Liver surgeries: Liver resections
Gynecologic procedures: Staging for ovarian Cancer, Radical Hysterectomies