ANESTHESIOLOGY

Computer-assisted Individualized Hemodynamic Management Reduces Intraoperative Hypotension in Intermediate- and High-risk Surgery: A Randomized Controlled Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Hemodynamic management strategies bracketing predetermined ranges of arterial pressure and flow variables have been demonstrated to reduce certain perioperative complications
- Individualized hemodynamic management using closed-loop control of blood pressure and a decision support system for fluid titration appears feasible using proprietary monitors and software

What This Article Tells Us That Is New

- The authors demonstrate in a prospective randomized trial of 38 intermediate- or high-risk patients undergoing abdominal or orthopedic surgery that a closed-loop system titrating a norepinephrine infusion based on an invasive arterial pressure monitoring system alongside a separate decision support system using mini-fluid challenges results in a significant decrease in the percentage of intraoperative time with a mean arterial pressure less than 90% of the patients preoperative baseline value when compared to the same approach applied manually

ABSTRACT

Background: Individualized hemodynamic management during surgery relies on accurate titration of vasopressors and fluids. In this context, computer systems have been developed to assist anesthesia providers in delivering these interventions. This study tested the hypothesis that computer-assisted individualized hemodynamic management could reduce intraoperative hypotension in patients undergoing intermediate- to high-risk surgery.

Methods: This single-center, parallel, two-arm, prospective randomized controlled single blinded superiority study included 38 patients undergoing abdominal or orthopedic surgery. All included patients had a radial arterial catheter inserted after anesthesia induction and connected to an uncalibrated pulse contour monitoring device. In the manually adjusted goal-directed therapy group (N = 19), the individualized hemodynamic management consisted of manual titration of norepinephrine infusion to maintain mean arterial pressure within 10% of the patient's baseline value, and mini-fluid challenges to maximize the stroke volume index. In the computer-assisted group (N = 19), the same approach was applied using a closed-loop system for norepinephrine adjustments and a decision-support system for the infusion of mini-fluid challenges (100 ml). The primary outcome was intraoperative hypotension defined as the percentage of intraoperative case time patients spent with a mean arterial pressure of less than 90% of the patient's baseline value, measured during the preoperative screening. Secondary outcome was the incidence of minor postoperative complications.

Results: All patients were included in the analysis. Intraoperative hypotension was 1.2% [0.4 to 2.0%] (median [25th to 75th] percentiles) in the computer-assisted group compared to 21.5% [14.5 to 31.8%] in the manually adjusted goal-directed therapy group (difference, –21.1 [95% CI, –15.9 to –27.6%]; $P < 0.001$). The incidence of minor postoperative complications was not different between groups (42 *vs.* 58%; $P = 0.330$). Mean stroke volume index and cardiac index were both significantly higher in the computer-assisted group than in the manually adjusted goal-directed therapy group ($P < 0.001$).

Conclusions: In patients having intermediate- to high-risk surgery, computer-assisted individualized hemodynamic management significantly reduces intraoperative hypotension compared to a manually controlled goal-directed approach.

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Intraoperative hypotension occurs frequently and negatively affects postoperative outcomes.[1,2] Using large analyses, several research groups have reported a significant relationship between intraoperative hypotension during noncardiac surgery and postoperative complications.[3–10] The incidence of these complications appears to be related to the magnitude and the duration of the hypotension. Specifically, only 1 min with a mean arterial pressure (MAP) less than 55 to 65 mmHg intraoperatively has been associated with a higher risk of morbidity.[3] In a multicenter, randomized controlled trial, Futier *et al.*[11] demonstrated that maintaining an "individualized" arterial pressure during surgery (within 10% of the patient's baseline reference value) reduced postoperative organ dysfunction compared to standard management. This was achieved using a continuous norepinephrine infusion started at anesthesia induction

and continued until the end of surgery. After this study, this approach is being used by several teams around the world to minimize intraoperative hypotension during high-risk surgery. However, the use of vasoconstrictors to maintain an individualized arterial pressure may mask the development of hypovolemia, exposing patients to risks associated with reduced end organ blood flow.

Optimizing flow and pressure requires repeated measurement of both variables and use of established protocols for vasopressor and fluid administration. This strategy, called "individualized hemodynamic management," has been shown to be associated with decreased postoperative complications compared to routine care.[12] However, efficient and accurate control of MAP and cardiac output is a challenge during major surgery, because it requires frequent manual adjustments of vasopressor infusion rates and timely fluid administration, thus necessitating continuous attention of the care provider, which can prove difficult to achieve.

We have developed closed-loop systems for automated vasopressor and fluid administration.[13–17] When used separately, these systems have been shown to be more effective at maintaining hemodynamic targets (MAP and stroke volume [SV] index) than manual management for patients undergoing major surgery.[13,18] Unfortunately, a "single" closed-loop system allowing the simultaneous coadministration of vasopressors and fluid is not currently available for widespread clinical use, although we are actively working on its development. An important step in this process is the combination of a closed-loop system for vasopressor administration and a decision-support system for bolus fluid administration.

The hypothesis for this prospective randomized controlled study was therefore to demonstrate that patients managed using a computer-assisted system would experience less intraoperative hypotension (defined as a MAP less than 90% of the patient's baseline value) during intermediate- to high-risk surgery when compared to patients in whom vasopressor and fluid administration were controlled manually.

This article is featured in "This Month in Anesthesiology," page A1. This article is accompanied by an editorial on p. 203. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has a video abstract. This article has a visual abstract available in the online version.

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Materials and Methods

This single-center, prospective, two-arm, parallel, randomized controlled superiority study was approved by the institutional review board of Bordeaux (Comité de Protection des Personnes Sud-Ouest et Outre Mer III, Bordeaux, France No. DC2015/117), and the study protocol was published on clinicaltrials.gov (NCT03965793) on May 29, 2019, before patient enrollment began (Principal Investigator: Alexandre Joosten). Importantly, since 2018, clinical research protocols are not reviewed by the local institutional review board but rather are randomly directed to a different institution's review board in France to reduce bias in reviews. The study was conducted at Bicêtre Hospital from October 28, 2019, through June 26, 2020. All patients were approached by the principal investigator, and after presentation of the study purposes, written informed consent was obtained before inclusion.

Inclusion and Noninclusion Criteria

Adult patients scheduled for an elective intermediate- to high-risk abdominal or orthopedic surgical procedure[19] who were expected to be managed according to an individualized hemodynamic protocol using a radial catheter coupled to an advanced hemodynamic monitoring device (EV1000, Edwards Lifesciences, USA) as part of their anesthetic care were eligible for this protocol. Noninclusion criteria were minor patients (less than 18 years old), pregnancy, cardiac arrhythmias, and refusal to participate. The trial was conducted in accordance to the original protocol, and as a result, no change has been made in the protocol after trial commencement.

Randomization and Blinding

Randomization assignments were generated without restriction and were generated on October 24, 2019, by our res earch nurse using an internet-based software (http://www.randomization.com), to either closed-loop vasopressor and decision-support–guided fluid therapy (computer-assisted group) or manually adjusted goal-directed therapy group. Opaque envelopes in recruitment sequence were then created by an unaffiliated research nurse. The morning of the surgery, a sealed opaque envelope containing the assigned patient number was opened. The envelopes were kept in the research office of Bicêtre Hospital. Patients were blinded to group allocation, but anesthesia providers were not. However, outcome data were collected by collaborators blinded to both the study group allocation and the reasoning for the research protocol. Importantly, as stipulated by the institutional review board, the principal investigator could not be the primary anesthesiologist but should be present to supervise the computer-assisted systems. Patients in the manually adjusted goal-directed therapy group were managed by an anesthesiologist not involved in the current study who applied the individualized hemodynamic

protocol (manually) that is routine in our institution for these surgical procedures (fig. A1).

Anesthesia Procedure

Preoperatively, all patients stopped taking angiotensin-converting enzyme inhibitor drugs and/or angiotensin receptor blocker drugs 48 h before surgery per institutional standard of care. Standard monitoring was applied to all patients and included a three-lead electrocardiogram, non-invasive pulse oximetry, standard arm arterial pressure cuff, capnography, central temperature assessment (esophageal probe) and a depth of anesthesia monitor (BIS, Medtronic, France). A radial artery catheter was also inserted during induction and linked *via* a Flotrac sensor to a pulse contour analysis hemodynamic monitor (EV1000). Anesthesia was induced with sufentanil (2 μg/kg) and propofol (2 mg/kg). Atracurium (0.6 mg/kg) was administered for intubation, and 10-mg boluses were added as needed to maintain the train-of-four ratio less than 2 (TOF Scan Technology, Idmed, France). Anesthesia was maintained with sevoflurane to keep a BIS value between 40 and 60. Sufentanil boluses (0.1 to 0.2 μg/kg) could be administered at the discretion of the primary anesthesia provider. All patients received mechanical ventilation using a volume control mode with tidal volumes of 7 to 8 ml/kg of predicted body weight and a respiratory rate adjusted to achieve an end tidal carbon dioxide between 34 and 38 cm H_2O. Recruitment maneuvers were done at the discretion of the anesthesiologist in charge of the patient. Prophylactic antibiotics and antiemetics were administered 30 min before surgical incision.

It is common practice in our hospital that fluid management for intermediate- to high-risk abdominal and orthopedic surgical patients be standardized This is achieved with a baseline maintenance infusion of Ringer's lactate solution (Fresenius Kabi, France) set at a rate of 2 to 4 ml · kg^{-1} · h^{-1} (laparoscopic *vs.* open) and additional fluid boluses based on an advanced uncalibrated hemodynamic device (EV1000). This monitor provides flow-based variables (SV index and cardiac index) and SV variation, a dynamic predictor of fluid responsiveness. To avoid intraoperative hypothermia, a forced-air warming system (Bair Hugger, SEBAC, France) and a blood-fluid warming system (Fluido compact, SEBAC, Flaxlanden) were utilized during the surgical procedure. Packed red blood cells were infused to maintain the hemoglobin concentration between 7 and 9 g/dl, depending on each patient's status and comorbidities.

For postoperative pain management, all patients who had a laparotomy had a thoracic epidural catheter inserted by the anesthesiologist before induction. The epidural was activated after a test dose (4-ml lidocaine 2% with 1:200,000 epinephrine) and was infused with ropivacaine 2 mg/ml in a bag of 200 ml of normal saline into which 10 mg of morphine was added. The mixture was infused at a rate of 5 to 6 ml/h from skin incision until postoperative day 3.

Individualized Fluid and Vasopressor Administration Protocol

In the manually adjusted goal-directed therapy group, vasopressor and fluid administration was adjusted manually by anesthesia providers and/or nurse anesthetists using our institutional individualized hemodynamic protocol. This protocol consists of two main components: (1) individualized MAP control starting at anesthesia induction and continued until the end of the surgery and (2) SV index maximization using mini-fluid challenges of 100-ml fluid boluses. Details regarding this individualized hemodynamic protocol are shown in figure A1.

In the computer-assisted group, the same strategy was applied but using a computer-assisted system including the following:

1. A closed-loop vasopressor system was used to titrate vasopressor administration. Details on this system are described in our previous publications[16,17,20–23] and in the online Supplemental Digital Content 1 (http://links.lww.com/ALN/C620). As review, MAP values from an EV1000 monitor were collected by the closed-loop vasopressor, and the proportional, integral, and derivative errors (if any) were converted into a dose titration of a norepinephrine infusion. The closed-loop vasopressor controller itself is a hybrid proportional integral derivative and rules-based system. The algorithm was coded in Visual C (Microsoft, USA), and software version 2.93 of the closed-loop system was used exclusively for patients enrolled in the computer-assisted group. The system was run on an Acer (Taiwan) laptop using Windows 7 (Microsoft). It collected MAP data from the EV1000 monitor *via* a serial RS232 connection and controlled a Chemyx Fusion 100 syringe pump (Chemyx Inc., USA) *via* USB. Importantly, a second norepinephrine syringe not associated with the system was also available to the primary team if the system experienced errors or for emergency use. Per protocol, the primary team was only to give "rescue" boluses of vasopressors in the event the system performance was inadequate.
2. A real-time clinical decision support system called "assisted fluid management" (AFM, Edwards Lifesciences) was used to guide mini-fluid challenges. Briefly, this system suggests to the anesthesia provider that a fluid bolus should be administered, analyzes the effects of the bolus, and continually reassesses the patient for further fluid requirements.[24] The AFM algorithm core is the same as the closed-loop algorithm we used in previous publications; 100% compliance with the AFM prompts would result in identical treatment that achieved by closed-loop control, although with minimal time delays for acceptance of recommendations. Figure 1 presents the schematic for the computer-assisted group. In both groups, the norepinephrine infusion was administered through an intravenous line not used for any other purpose.

Figure A2 shows the computer-assisted set-up in the operating room at Bicêtre Hospital. Importantly, in both groups, no other vasopressor than norepinephrine was allowed.

Outcome Measures

The primary outcome measure was intraoperative hypotension defined as the percentage of intraoperative case time patients spent with a MAP less than 90% of the patient's baseline value, measured during the preoperative screening. This cutoff has been chosen based on the implementation of our individualized hemodynamic protocol already in place in our institution a few months before the beginning of the current study. The primary outcome was calculated on a per-patient basis as follows:

$$\%\ hypotension = \frac{Minutes\ of\ case\ time\ with\ MAP < 90\%\ baseline}{Total\ minutes\ of\ case\ time}$$

It was assumed that with the modest sample size, we would be unlikely to see differences in major complications, so our secondary outcome measure was the incidence of minor postoperative complications measured at postoperative day 30 (including postoperative nausea and vomiting, delirium, wound infection, urinary infection, pneumonia, acute kidney injury, paralytic ileus, other infections, and readmission to hospital within 30 days postsurgery). These complications have been defined in our previous publications.[25,26]

Other hypothesis-generating outcome measures included major complications (at postoperative day 30), percentage of case time with a MAP less than 65 mmHg, percentage of case time "in target" (MAP ± 10 mmHg of the baseline MAP), percentage of case time above target (MAP greater than 10 mmHg), mean SV variation, cardiac index, SV variation, SV index during the first and last 30 min of the case, and the percentages of case time with a SV variation less than 13%, with a cardiac index less than 2 l · min^{-1} · m^{-2}, and with a SV index less than 30 ml · m^{-2}.

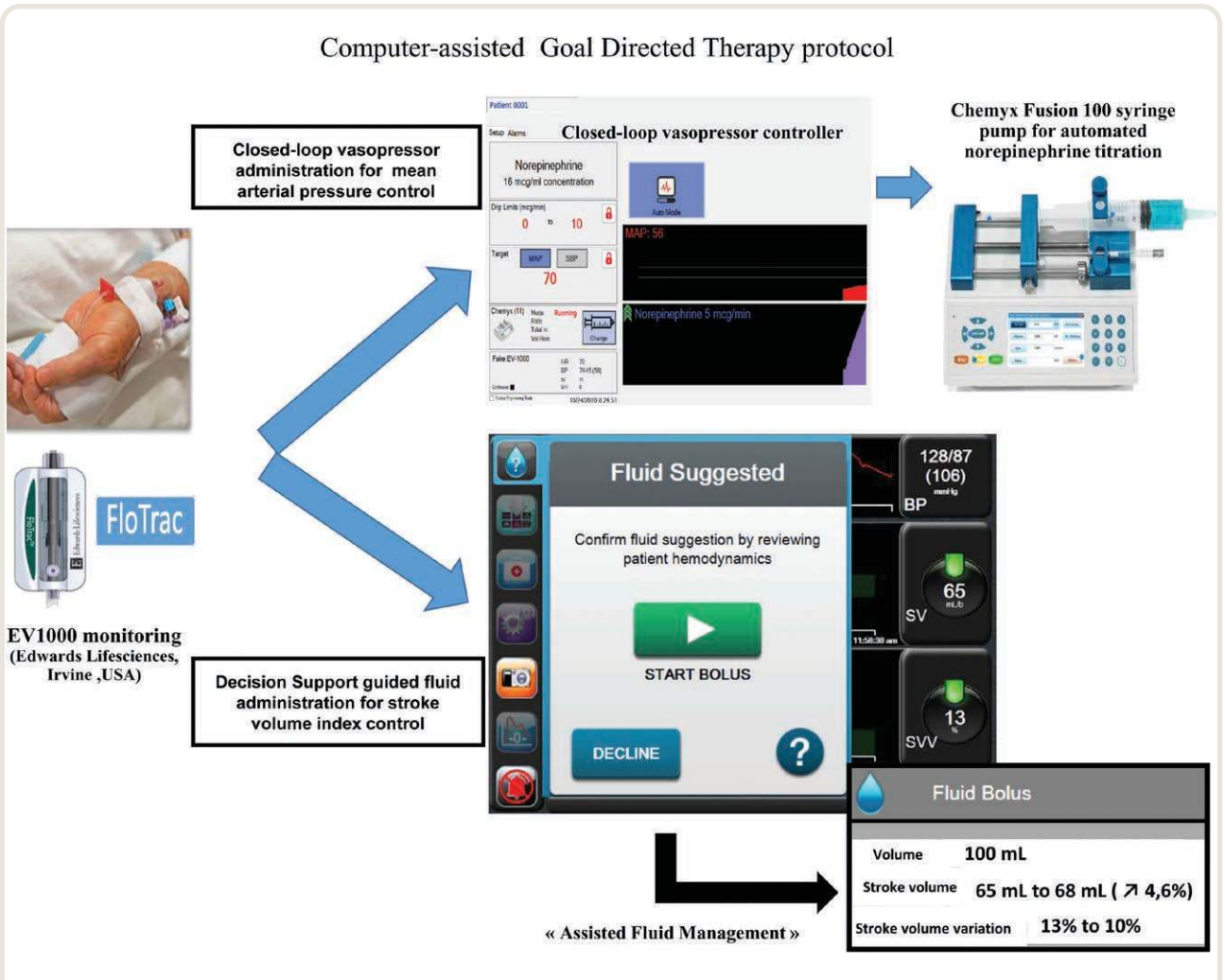

Fig. 1. Schematic representation of our computer-assisted individualized hemodynamic management protocol. Chemyx Fusion 100 syringe pump (Chemyx Inc., USA).

We also recorded total intraoperative volumes of fluids administered, net fluid balance, total doses of norepinephrine given, the number of norepinephrine rate modifications during surgery, lactate values measured before skin incision and at arrival in the postanesthesia care unit, and lengths of stay in the postanesthesia care unit, intensive care unit, and the hospital. No change in the outcomes has been made after trial commencement.

Data Collection

All hemodynamic variables were collected at 20-s intervals *via* the EV1000 monitor. The study started once the radial artery catheter had been inserted and connected to the EV1000 monitor, approximately 5 min after anesthesia induction.

Study Power

Power calculation was performed based on the primary objective. Our data showed that patients spent 12 ± 8% of intraoperative case time with a MAP of less than 90% of their preoperative value when norepinephrine was titrated manually.[27] To detect a 50% reduction in the time spent in hypotension in the computer-assisted group, the study needed 19 patients/group (38 patients total) to achieve 80% power with Welch's unequal variances *t* test and bilateral α risk fixed at 5%. No dropout was taken into account.

Statistical Analysis

The data were analyzed using an intention-to-treat approach and in a blinded fashion. Normality of data was evaluated using the Kolmogorov–Smirnov test. Variables normally distributed were compared with independent samples *t* test and are expressed as means ± SD. Nonnormally distributed variables were compared with a Mann–Whitney U test and were expressed as median [25% to 75%] percentiles. Discrete data are expressed as numbers and percentages and were compared using a chi-square or Fisher's exact test when indicated.

The primary outcome was evaluated using a Mann–Whitney U test; differences between groups with 95% CI were also calculated. The secondary outcomes were evaluated using a chi-square test. The analyses were not adjusted for additional variables. No interim analysis was planned on the data. Statistical significance was set at $P < 0.05$, and all tests were two-tailed. Analyses were performed using Minitab (France).

Results

Patient Population

Between October 28, 2019, and June 26, 2020, 133 patients were screened for eligibility, and 38 patients were enrolled and randomized. As a result, the trial was not stopped before obtaining the sample size goal. Reasons for noninclusion are shown in figure 2. All patients were included in this intention to treat analysis.

Preoperative and Intraoperative Data

Patients in both groups had similar baseline MAP. Importantly, there were no differences between groups in the numbers of patients undergoing a laparoscopic surgery or having a thoracic epidural analgesia (table 1).

There were no significant differences between groups in anesthesia duration, baseline fluid infusion, or the total volume of fluid boluses received (table 2). However, estimated blood loss and urine output were significantly higher in the computer-assisted group than in the manually adjusted goal-directed therapy group. Consequently, the net fluid balance at the end of the surgery was significantly lower in the computer-assisted group than in the manually adjusted goal-directed therapy group (table 2). The total dose of norepinephrine was more than 40% lower in the computer-assisted group than in the manually adjusted goal-directed therapy group. The computerized closed-loop vasopressor system made more than 1,000 modifications of the infusion rate per case compared to a median of 15 in the manually adjusted goal-directed therapy group (table 2).

Outcomes

The primary outcome, *i.e.*, the percentage of intraoperative case time a patient had hypotension (defined as a MAP less than 90% of their baseline MAP) was 1.2% [0.4 to 2.0] in the computer-assisted group compared to 21.5% [14.5 to 31.8] in the manually adjusted goal-directed therapy group (difference, −21.1 [95% CI, −15.9 to −27.6]; $P < 0.001$; table 3). The percentage of intraoperative case time with a MAP less than 65 mmHg was also lower in the computer-assisted group than in the manually adjusted goal-directed therapy group (0.0% [0.0 to 0.0] *vs.* 1.9% [1.2 to 5.0]; $P < 0.001$). Patients in the computer-assisted group were within the target MAP range (± 10 mmHg of their baseline MAP value) for a greater percentage of time than those in the manually adjusted goal-directed therapy group (97.2% [95.0 to 97.7] *vs.* 58.8% [48.3 to 70.5]; $P < 0.001$). The percentage of time with *hyper*tension (defined as a MAP greater than10 mmHg of the MAP target) was also lower in the computer-assisted group than in the manually adjusted goal-directed therapy group (2.5% [1.5 to 4.9] *vs.* 12.9% [5.7 to 22.8]; $P = 0.001$; table 4). A heat map of MAP error and stroke volume index by group for all patients is shown in figure 3. The MAP error relative to target MAP in all 38 cases is given in figure A3.

All flow-based variables were better maintained within optimal targets during surgery in the computer-assisted group than in the manually adjusted goal-directed therapy group despite a greater estimated blood loss during surgery in the computer-assisted group. There was no significant

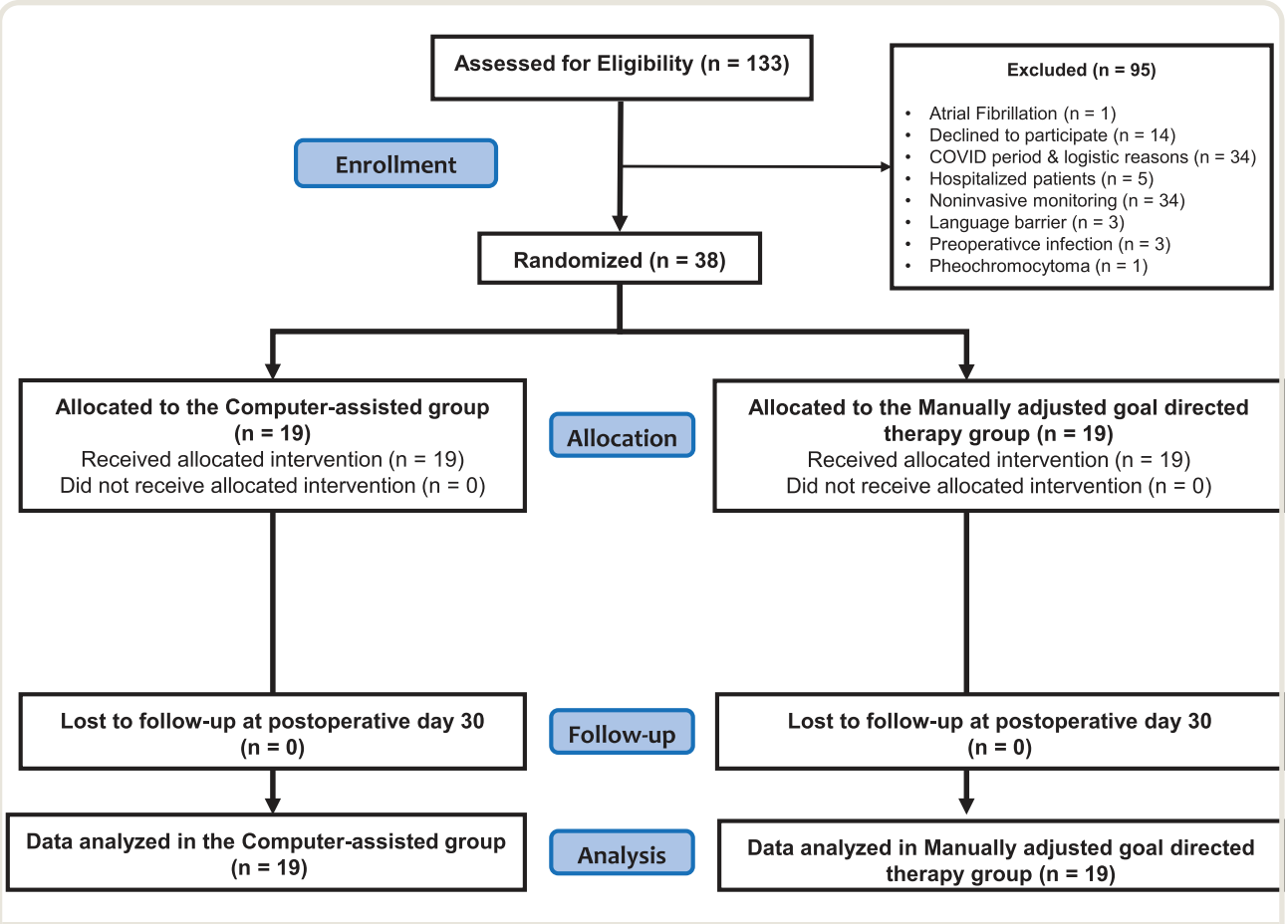

Fig. 2. Consolidated Standards of Reporting Trials diagram of patient flow.

difference in baseline SV index between groups, but the average SV index during the last 30 min of the case was significantly higher in the computer-assisted group than in the manually adjusted goal-directed therapy group ($P = 0.001$). Figure A4 shows SV index in all patients. Importantly, we did not have any missing data among the primary and secondary outcomes.

Lactate concentration at the beginning of the surgery was similar in the two groups, but on arrival in the postanesthesia care unit, patients in the computer-assisted group had a lower lactate concentration than those in the manually adjusted goal-directed therapy group (1.2 [0.9 to 2.3] μmol/L *vs.* 2.7 [1.6 to 3.2] μmol/L; $P = 0.011$; table 2). The incidence of postoperative minor complications (secondary outcome) was not different between groups (computer-assisted: 42%; control: 58%; mean difference 16% [95% CI, −16 to 48]; $P = 0.330$; table 3). Major complications, as well as lengths of stay (postanesthesia care unit, intensive care unit, or hospital), were similar between groups (table 4). No patient died within 30 days postsurgery.

The closed-loop vasopressor system did not experience any technical failures during use, and the anesthesiologists in the computer-assisted group never used backup vasopressor options throughout the surgery. Lastly, the second norepinephrine infusion was never used in the computer-assisted group.

Discussion

The current study demonstrates that use of computer-assisted hemodynamic management clearly outperforms standard hemodynamic management in intermediate-and high-risk abdominal and orthopedic surgery. Patients in the computer-assisted group had less hypotension, less hypertension, higher mean cardiac index and SV index, and lower lactate concentrations on arrival in the PACU. When using the usual "population" definition of hypotension (MAP less than 65 mmHg), patients in the computer-assisted group had no detectable hypotension. Moreover, these results occurred despite twice the amount of blood loss in the computer-assisted group compared to the manually adjusted goal-directed therapy group. In addition to all the differences noted above, the computer-assisted group also had lower positive net fluid balance at the end of surgery and a higher end-case SV index.

Table 1. Patient's Baseline Characteristics

Variable	Control (N = 19)	Computer-assisted (N = 19)
Age, yr	63 ± 15	64 ± 13
Male, No. (%)	12 (63)	15 (79)
Weight, kg	70 ± 15	79 ± 18
Height, cm	169 ± 12	171 ± 9
Body mass index, kg/m^2	24 ± 5	27 ± 5
Patients with ASA status II or III, No. (%)	14 (74)/5 (26)	9 (47)/10 (53)
Preoperative hemoglobin, g/dl	13.1 ± 1.8	13.1 ± 1.7
Preoperative creatinine, mmol/l	73.3 ± 18.9	84.1 ± 28.6
Preoperative MAP, mmHg	90 [85 to 90]	90 [85 to 90]
Minimum MAP target for surgery, mmHg*	81 [76 to 81]	81 [76 to 81]
Medications, No. (%)		
Aspirin	0 (0)	6 (32)
β-Blocker	3 (16)	5 (26)
Angiotensin-converting enzyme inhibitor	3 (16)	4 (21)
Angiotensin II receptor blockers	0 (0)	2 (11)
Statin	1 (5)	2 (11)
Calcium blocker	3 (16)	4 (21)
Hypoglycemic agent	1 (5)	6 (32)
Comorbidities, No. (%)		
Myocardial injury	0 (0)	2 (11)
Hypertension	6 (32)	11 (58)
Hyperlipidemia	1 (5)	3 (16)
Diabetes	1 (5)	7 (37)
Type of surgery, No. (%)		
High-risk abdominal surgery	11 (58)	11 (58)
Moderate-risk abdominal surgery	6 (32)	5 (26)
High-risk orthopedic surgery	2 (11)	3 (16)
Laparoscopic surgery, No. (%)	6 (31)	4 (21)
Thoracic epidural analgesia, No. (%)	13 (68)	13 (68)

The data are presented as means ± SD, median and [25 to 75] percentiles or number and percentage.

*The minimum MAP target is the minimal MAP to be maintained by anesthesiologists in charge of the patient, defined as preoperative MAP – 10%

ASA, American Society of Anesthesiologists; MAP, mean arterial pressure.

One concern with targeting an individualized MAP during surgery may be that cardiac output (flow) may be sacrificed at the expense of pressure and that hypovolemia may not be corrected if it is hidden by a blood pressure considered as acceptable. However, patients in the computer-assisted group exhibited statistically superior flow-based measures than those in the manually adjusted goal-directed therapy group. The lower postoperative lactate concentrations in the computer-assisted group compared to the manually adjusted goal-directed therapy group suggest that the balance between oxygen transport and oxygen consumption was maintained better in the former group.

Although the incidence of postoperative complications was not significantly different in the two groups, the higher incidence of superficial wound infection in the manually adjusted goal-directed therapy group could reflect less optimal tissue oxygenation in these patients. A larger study is necessary to evaluate the effect of this strategy on postoperative complications.

Individualized hemodynamic management (previously called "goal-directed hemodynamic therapy") has been associated with improved patient outcomes compared to routine care during major surgery, as recently confirmed by two meta-analysis.[28,29] Futier *et al.*[11] also reported that "individualized" arterial pressure management resulted in less postoperative organ dysfunction. More recently, Nicklas *et al.*[12] demonstrated that individualizing hemodynamic management by using patient baseline cardiac index value as a target to guide fluid administration resulted in fewer postoperative complications. However, adoption of these strategies by clinicians has been slow, and even if used during surgery, results may be limited because of poor protocol compliance. Computer-assisted systems may present a bridge between implementing the evidence-based intervention and ensuring compliance, reducing provider workloads while delivering consistent high-compliance therapy that is still directed by the physician. Moreover, the "packaging" of goal-directed strategies into a device reduces the barrier to implementation. Indeed, computer systems are designed for highly repetitive and attention-dependent tasks but thankfully do not suffer with problems associated with vigilance fatigue. Therefore, computational systems are consistently more accurate at maintaining a target set point than anesthesia providers. Moreover, the choice of target set points, and indeed whether a given patient should be placed on a protocol in the first place, are decisions that appropriately remain in the hands of the clinicians. As a result, we believe that automated systems are the best option for automation of noncognitive tasks moving forward.[30,31]

Our study has several limitations that should be considered. First, the principal investigator supervised the computer systems for each patient in the computer-assisted group (in addition to the primary anesthesia provider). This is an impractical setup for widespread adoption, so assurance that the system can be used effectively and safely by a wide range of providers will be necessary for dispersed use. Second, the presence of this additional investigator in the operating room also has the potential to confound the results collected (Hawthorne effect), although the interventions in the "computer-assisted group" are mostly decided by the automated systems in place and will unlikely succumb to any significant observation bias. Similarly, because the primary anesthesia care provider in the manually adjusted group was not involved in the current study, it cannot be ruled out that they were less focused at optimizing hemodynamic status than if they were aware of the study purpose. The specific providers present and level of training (*i.e.* nurse anesthetists, residents of different years, faculty of different levels of experience) in individual cases was not controlled in the current study. It is possible that some effect caused by group differences in these dimensions may have been overlooked, although the randomization of assignment should have mitigated this. Third, we were unable to record the amount of surgical time each

Table 2. Intraoperative Data

Variables	Manually Adjusted Goal-directed Therapy Group (N = 19)	Computer-assisted Goal-directed Therapy Group (N = 19)	*P* Value
Anesthesia duration, min	340 [260 to 480]	330 [280 to 435]	0.493
Surgery duration, min	265 [190 to 370]	240 [210 to 359]	0.651
Baseline maintenance crystalloid, ml	1,487 ± 751	1,608 ± 723	0.616
Total volume of fluid bolus (crystalloid and colloid), ml*	1,937 ± 1,024	1,753 ± 857	0.551
Packed red blood cells, ml	721 ± 315	331 ± 129	0.070
Patients transfused, %	3 (16)	4 (21)	0.676
Total IN, ml	2,600 [2,250 to 5,000]	3,300 [2,800 to 4,200]	0.770
Estimated blood loss, ml	400 [200 to 550]	1,000 [400 to 1,500]	**0.022**
Urine output, ml	400 [300 to 500]	950 [600 to 1,200]	**0.002**
Gastric suction, ml	100 [50 to 100]	150 [100 to 250]	**0.049**
Total OUT, ml	800 [600 to 1,150]	1,900 [1,150 to 3,002]	**0.002**
Fluid balance, ml	2,050 [1,650 to 4,060]	1,400 [700 to 2,100]	**0.034**
Mean BIS values	49.4 ± 3.2	49.6 ± 3.1	0.838
Total dose of norepinephrine, μg	1,340 [710 to 2,240]	765 [535 to 1,426]	0.068
Mean rate of norepinephrine, $\mu g \cdot min^{-1}$	5.8 [2.7 to 9.1]	2.7 [2.0 to 6.7]	0.133
Norepinephrine rate modifications, No.	15 [12 to 20]	1,271 [999 to 1,432]	**< 0.001**
Percentage of case time when norepinephrine infusion was running	95 [95 to 95]	96 [91 to 99]	0.438
Lactate before skin incision, mEq/l	1.3 [0.8 to 1.9]	1.0 [0.9 to 1.5]	0.401
Lactate at PACU arrival, mEq/l	2.7 [1.6 to 3.2]	1.2 [0.9 to 2.3]	**0.011**

Total IN is the sum of crystalloid, colloid, and blood product administration, while total OUT is the sum of estimated blood loss, urine output, and gastric suction. Fluid balance is the difference between total IN – total OUT. BIS values are measured using the BIS depth of anesthesia monitor (Medtronic, France). The data are expressed as means ± SD, median and [25th to 75th] percentiles or number (%). Bold type indicates statistically significant *P* values.

*Only one patient received a colloid solution in the control group.

PACU, postanesthesia care unit.

Table 3. Primary and Secondary Outcome Variables

Variables	Manually adjusted Goal-directed Therapy group (N = 19)	Computer-assisted Goal-directed Therapy group (N = 19)	*P* Value
Primary outcome			
Intraoperative hypotension (%)*	21.5 [14.5 to 31.8]	1.2 [0.4 to 2.0]	**< 0.001**
Secondary outcomes			
Patients with minor complications, No. (%)†	11 (58)	8 (42)	0.330
Postoperative nausea and vomiting	1 (5)	3 (16)	0.290
Delirium/confusion	1 (5)	1 (1)	> 0.999
Acute kidney injury (Kidney Disease Improving Global Outcomes levels 1 to 3)	1 (5)	2 (11)	0.547
Superficial wound infection	5 (21)	1 (5)	**0.034**
Urinary infection	2 (11)	0 (0)	0.146
Other infections	2 (11)	4 (21)	0.374
Pneumonia	1 (5)	1 (5)	> 0.999
Paralytic ileus	5 (26)	4 (21)	0.703
30-day readmission to hospital	3 (16)	1 (5)	0.290

Data are expressed as number and percentage (%) or median [25th to 75th] percentiles

*Intraoperative hypotension defined as the percentage of case time with a mean arterial pressure that is less than 90% of the mean arterial pressure target. †Some patients had more than one minor complication.

patient was hypotensive during induction because our system required post induction arterial line placement. This is unfortunate, because recording these data would have enabled us to determine whether computer-assisted management functions well with hypotension after induction. Maheshwari *et al.*[32] demonstrated that approximately 30% of all hypotensive events occur during induction, so management of this period is an important consideration. Additionally, the MAP target chosen to define hypotension (MAP taken during the preoperative screening) could of course be challenged especially in view of the recent literature,[33] but it is the best and the most standardized we have in our institution. Fourth, our protocol was limited to intermediate- to high-risk abdominal and orthopedic

Table 4. Other Outcome Variables

Variable	Manually Adjusted GDT Group (N = 19)	Computer-assisted GDT Group (N = 19)	*P* Value
Mean stroke volume index, ml · m^{-2}	33.5 ± 7.5	40.9 ± 9.7	**0.012**
Stroke volume index first 30 min, ml · m^{-2}	34.8 ± 8.6	39.4 ± 9.6	0.129
Stroke volume index last 30 min, ml · m^{-2}	31.7 ± 8.4	42.1 ± 10.0	**0.001**
Mean cardiac index, l · min^{-1} · m^{-2}	2.4 ± 0.4	3.2 ± 0.6	**< 0.001**
Mean stroke volume variation, %	9.6 [7.6 to 12.5]	7.3 [6.5 to 9.6]	**0.022**
Percentage of case time with			
Stroke volume index less than 30 ml · m^{-2}	22.6 [10.6 to 57.2]	1.7 [0.0 to 31.5]	**0.030**
Cardiac index less than 2 l · min^{-1} · m^{-2}	21.6 [1.4 to 38.0]	1.5 [0.0 to 3.7]	**0.001**
Stroke volume variation less than 13%	76.6 [60.8 to 88.3]	96.1 [86.6 to 99.2]	**0.001**
MAP ± 10 mmHg of MAP target	58.8 [48.3 to 70.5]	97.2 [95.0 to 97.7]	**< 0.001**
MAP greater than 10 mmHg of MAP target	12.9 [5.7 to 22.8]	2.5 [1.5 to 4.9]	**0.001**
MAP less than 65 mmHg	1.9 [1.2 to 5.0]	0.0 [0.0 to 0.0]	**< 0.001**
MAP less than 60 mmHg	0.4 [0.0 to 2.1]	0.0 [0.0 to 0.0]	**< 0.001**
MAP less than 55 mmHg	0.0 [0.0 to 0.6]	0.0 [0.0 to 0.0]	**0.027**
Patients with any major complication, No. (%)*	5 (26)	2 (10)	0.209
Anastamotic leakage	2 (11)	1 (5)	0.547
Pulmonary edema	0 (0)	1 (5)	> 0.999
Reoperation	3 (16)	1 (5)	0.290
Bleeding	1 (5)	0 (0)	> 0.999
Atrial fibrillation	1 (5)	0 (0)	> 0.999
Postoperative hemoglobin, g · dl^{-1}†	10.8 ± 1.9	11.3 ± 2.0	0.479
Postoperative creatinine, mmol · l^{-1}†	76 [58 to 96]	76 [61 to 99]	0.540
PACU-ICU length of stay, h	9.0 [4.0 to 24.0]	9.0 [5.0 to 24.0]	0.988
Hospital length of stay, days	9.0 [6.0 to 16.0]	7.0 [5.0 to 16.0]	0.609

The data are expressed as number and percentage or median [25th to 75th] percentiles.

*Mortality at 30 days, stroke, renal replacement therapy, and pulmonary embolism were 0% in both groups. †Postoperative hemoglobin and creatinine were measured on postoperative day 1 or 2.

ICU, intensive care unit; MAP, mean arterial pressure; PACU, postanesthesia care unit.

surgical procedures and the current findings may not be broadly applicable to other surgeries or clinical settings (*e.g.*, cardiac surgery or intensive care unit). Fifth, the difference in blood loss between the groups is presumed to be random chance; bleeding episodes were surgical in nature and not caused by coagulopathy for example. The design of our study does not rule out the possibility that bleeding might actually be a result of our intervention and not random, however, so this is a question that will also need future study. There is a theoretical risk of increased blood pressure possibly leading to increased bleeding at the surgery site, although the benefits of increased perfusion may outweigh this potential risk. Of note, patients in the manually adjusted goal-directed therapy group spent more time during the procedure with a MAP greater than 10 mmHg above the individualized target. We also cannot rule out an observer effect in the computer-assisted group impacting estimated blood loss estimates, although this difference in estimated blood loss might have been related to the fact that more patients in the computer-assisted group were treated with aspirin.

Future Directions

A key consideration for fully automated hemodynamic management is that multiple factors can influence MAP. An ideal computer-assisted hemodynamic management system should be informed not just of current pressure, but also intravascular volume, anesthetic depth, some measure of sympathetic inhibition, heart rate, and cardiac function. Although our closed-loop system can tightly control MAP, it is not sufficient to rely solely on such a system to ensure adequate hemodynamic management. Looking forward, a holistic hemodynamic management system should be able to monitor and modify all the factors implicated in hemodynamic status. Implementation of such systems in clinical practice will still take time; there are many technological, practical, and regulatory considerations. That said, independently operating automated systems have been reported that manage hypnosis, analgesics, and fluid and vasopressor administration. There are even recent experiments using several systems simultaneously.[34–36] Given all these technological advances in computing power, it is evident that we will see much more of this work in the years to come.[37] Specifically regarding fully automated systems for both fluid and vasopressor administration, there is only one team (to our knowledge) that has designed such a system, although it is still experimental.[38,39] Our team is also actively working on the development of such a system.

Conclusions

In patients undergoing intermediate- and high-risk abdominal and orthopedic surgery, use of computer-

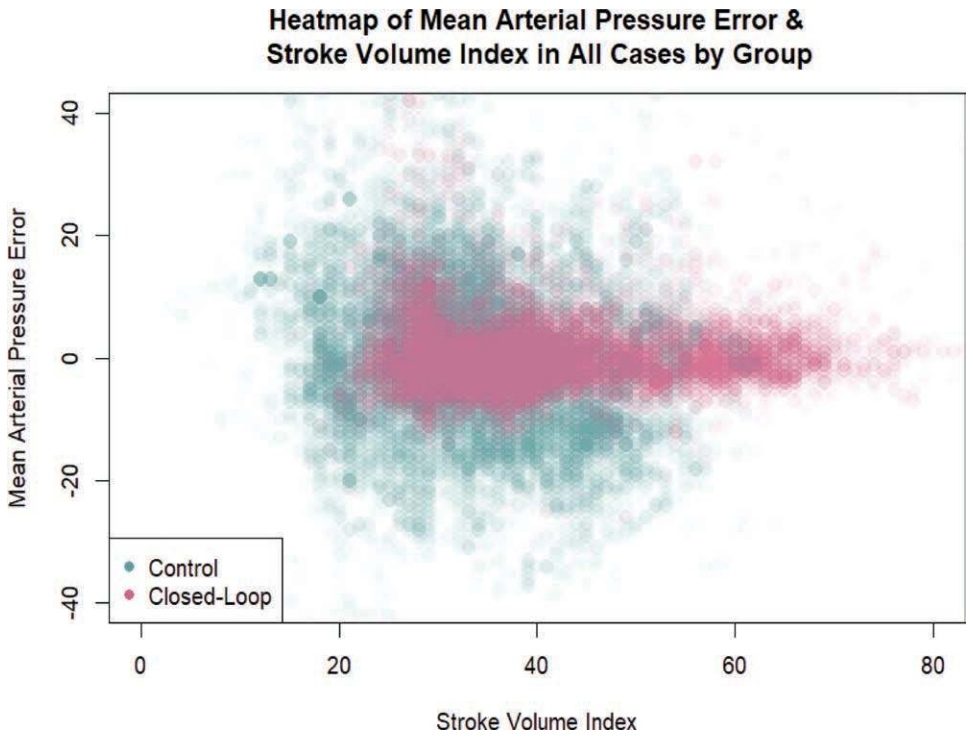

Fig. 3. Heat map of mean arterial pressure error and stroke volume index in all cases by group. A total of 34,000 data points are represented in the figure (three observations of mean arterial pressure/stroke volume index per minute per patient). The density of color in a location indicates the relative proportion of error for that combination of stroke volume index and mean arterial pressure error. The computer-assisted group error is visually clustered much more tightly than the manually adjusted goal-directed therapy group error around 0. Additionally, this figure illustrates higher stroke volume indexes in the computer-assisted group.

assisted individualized hemodynamic management significantly reduced intraoperative hypotension compared to the manually adjusted goal-directed therapy group. Computer-assisted systems can help anesthesia providers maintain adequate hemodynamic targets during surgery.

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Competing Interests

Dr. Cannesson, Dr. Joosten, and Dr. Rinehart are consultants for Edwards Lifesciences (Irvine, California) and have ownership interest in Perceptive Medical Inc. (Newport Beach, California), which is developing closed-loop physiologic management systems. In addition, Dr. Cannesson and Dr. Rinehart have ownership interest in Sironis (Newport Beach, California), which has developed a fluid closed-loop system that has been licensed to Edwards Lifesciences (Irvine, California) and was used in this study as a decision support system (assisted fluid management). The closed-loop system for vasopressor administration used in this study is new and is the sole creation of three of the authors (Dr. Cannesson, Dr. Rinehart, and Dr. Joosten). A provisional patent has been submitted through the University of California Irvine covering aspects of closed-loop vasopressor administration but does not cover any of the processes discussed in the current article. Dr. Van der Linden reports a financial relationship with Fresenius Kabi GMbH (Bad Homburg, Germany). Dr. Cannesson reports a financial relationship with Masimo (Irvine, California). Dr. Vicaut reports financial relationships with the following: Abbott

(Issy-les-Moulineaux, France), Bristol Myers Squibb (Rueil-Malmaison, France), Lilly (Neuilly-sur-Seine, France), Novartis (Rueil-Malmaison, France), Pierre Fabre (Boulogne Billancourt, France), Roche (Boulogne Billancourt, France), Astra Zeneca (Courbevoie, France), Bayer (Pontcarré, France), and Pfizer (Montrouge, France). The other authors declare no competing interests.

Reproducible Science

Full protocol available at: joosten-alexandre@hotmail.com or alexandre.joosten@aphp.fr. Raw data available at: joosten-alexandre@hotmail.com or alexandre.joosten@aphp.fr.

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Appendix

Individualized hemodynamic protocol at Bicetre Hospital

1) Initiation of norepinephrine infusion for anesthesia induction to keep MAP within 90% of patient's MAP baseline value during surgery without tolerating any MAP < 65 mmHg

2) Baseline Maintenance Fluid Administration of Ringer's Lactate: 2 ml/kg/h for laparoscopic surgery
4 ml/kg/h for laparotomy surgery

3) Start of the advanced hemodynamic monitoring after anesthesia induction

- Assessment of SV index
- Fluid boluses consisting of mini-fluid challenge of 100 ml Ringer's Lactate over 1 minute
- If patient is fluid responder (≥ 10% increase in SV index), continue mini-fluid challenge until SV index does not increase by > 10%
- SV index obtained after fluid maximization = SV index target
- If SV index decreases by > 10% from SV index target ➔ readministration of mini-fluid challenge
- Blood loss compensated (1:1) with Ringer's Lactate or colloid solution if necessary
- If despite norepinephrine + multiple mini-fluid challenge, cardiac index remains $< 2\ L.min^{-1}.m^{-2}$: : discussion about dobutamine titration
- Transfusion of one packed red blood cells unit to maintain a hemoglobin level > 7 g/dl
- Others: Assessment of arterial lactate & diuresis and maintenance of BIS level between 40-60

Fig. A1. Manual individualized hemodynamic protocol. BIS level is measured using the BIS depth of anesthesia monitor (Medtronic, France). MAP, mean arterial pressure.

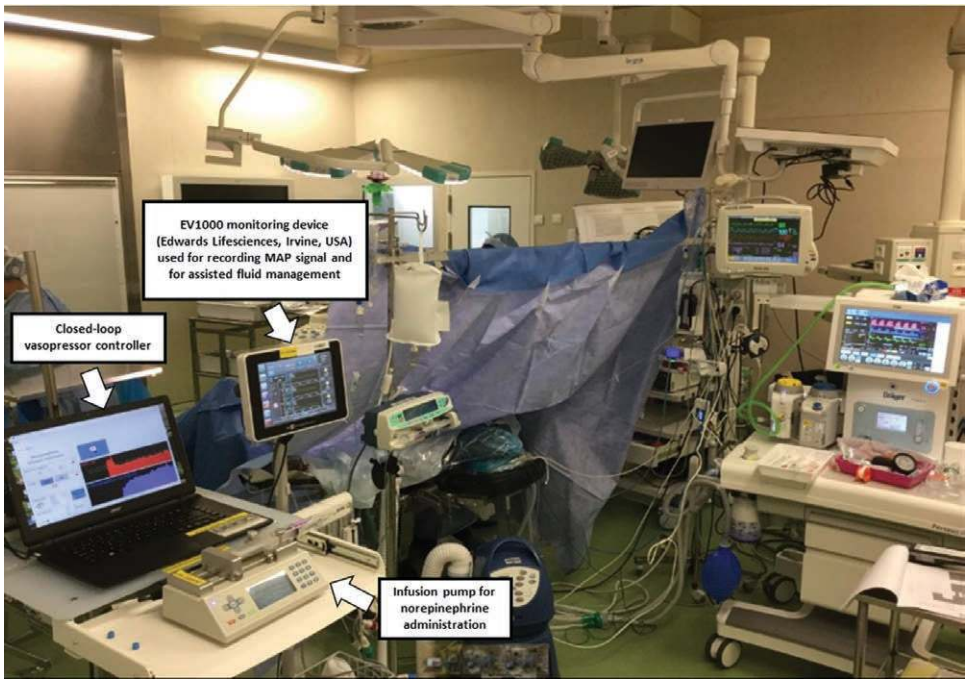

Fig. A2. Computer-assisted set-up in the operating room at Bicêtre Hospital, Le Kremlin-Bicêtre, France. MAP, mean arterial pressure.

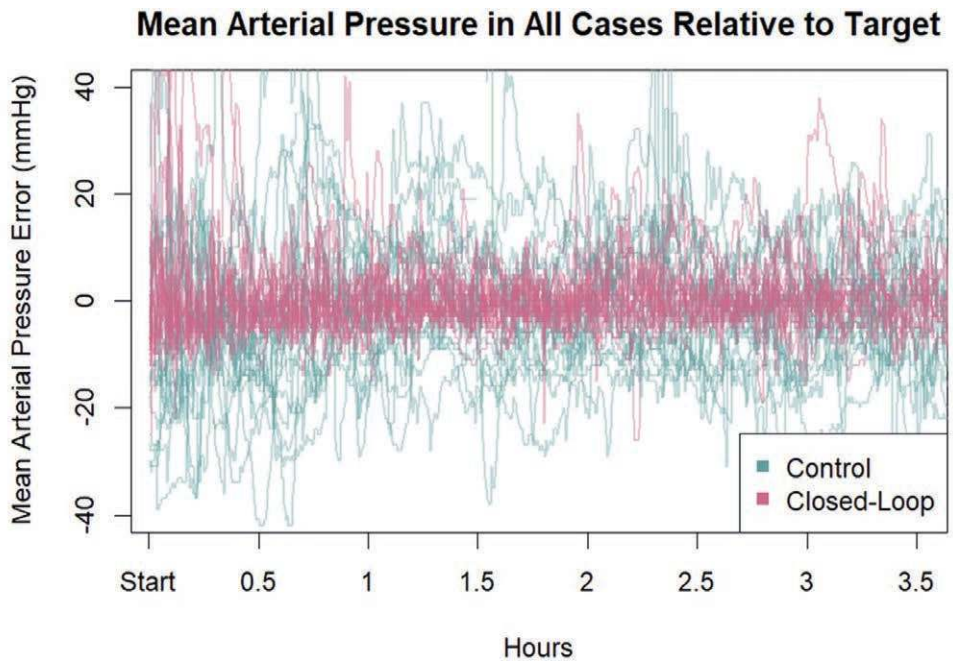

Fig. A3. Mean arterial pressure (mmHg) in all cases relative to target.

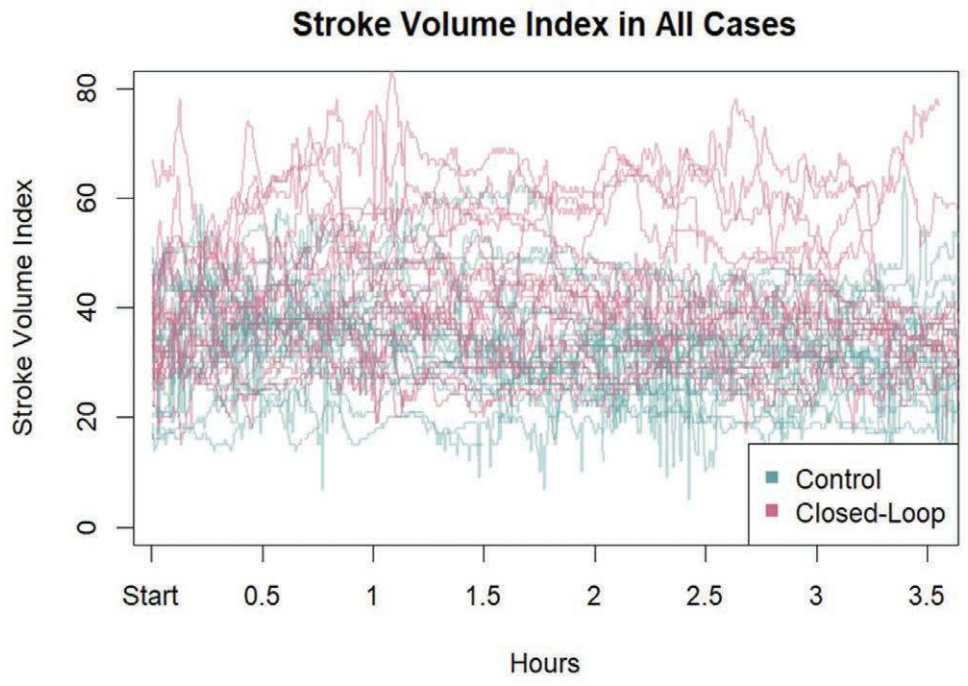

Fig. A4. Stroke volume index (ml · m^{-2}) in all cases.