ANESTHESIOLOGY

# Individualized Fluid Management Using the Pleth Variability Index

## A Randomized Clinical Trial

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## EDITOR'S PERSPECTIVE

### What We Already Know about This Topic

- The role of guided fluid management remains unclear, with contradictory trial results.
- The noninvasive plethysmographic variability index is one method of guiding fluid administration.

### What This Article Tells Us That Is New

- The investigators randomized 447 moderate-risk major arthroplasty patients to plethysmographic-guided *versus* routine fluid management.
- Fitness for discharge and actual hospital durations were essentially identical in each group. Complications were rare and similar in each group.
- Plethysmographic-guided fluid management did not reduce the duration of hospitalization or complications in moderate-risk surgery patients.

## ABSTRACT

**Background:** The present trial was designed to assess whether individualized strategies of fluid administration using a noninvasive plethysmographic variability index could reduce the postoperative hospital length of stay and morbidity after intermediate-risk surgery.

**Methods:** This was a multicenter, randomized, nonblinded parallel-group clinical trial conducted in five hospitals. Adult patients in sinus rhythm having elective orthopedic surgery (knee or hip arthroplasty) under general anesthesia were enrolled. Individualized hemodynamic management aimed to achieve a plethysmographic variability index under 13%, and the standard management strategy aimed to maintain a mean arterial pressure above 65 mmHg during general anesthesia. The primary outcome was the postoperative hospital length of stay decided by surgeons blinded to the group allocation of the patient.

**Results:** In total, 447 patients were randomized, and 438 were included in the analysis. The mean hospital length of stay ± SD was 6 ± 3 days for the plethysmographic variability index group and 6 ± 3 days for the control group (adjusted difference, 0.0 days; 95% CI, −0.6 to 0.5; $P = 0.860$); the theoretical postoperative hospital length of stay was 4 ± 2 days for the plethysmographic variability index group and 4 ± 1 days for the control group ($P = 0.238$). In the plethysmographic variability index and control groups, serious postoperative cardiac complications occurred in 3 of 217 (1%) and 2 of 224 (1%) patients ($P = 0.681$), acute postoperative renal failure occurred in 9 (4%) and 8 (4%) patients ($P = 0.808$), the troponin Ic concentration was more than 0.06 μg/l within 5 days postoperatively for 6 (3%) and 5 (2%) patients ($P = 0.768$), and the postoperative arterial lactate measurements were 1.44 ± 1.01 and 1.43 ± 0.95 mmol/l ($P = 0.974$), respectively.

**Conclusions:** Among intermediate-risk patients having orthopedic surgery with general anesthesia, fluid administration guided by the plethysmographic variability index did not shorten the duration of hospitalization or reduce complications.

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Among the 320 million patients who have surgery each year, the mortality rate remains between 0.5% and 4%,[1,2] and one in six patients experiences a postoperative complication, which increases the hospital length of stay and health cost.[3] Although perioperative goal-directed hemodynamic management has been widely shown to reduce postoperative complications in high-risk patients who have major surgery,[4] few data are available for intermediate-risk patients, who represent the majority of patients worldwide. Intermediate risk was defined based on the type of surgery[5] or the medical

This article is featured in "This Month in Anesthesiology," page 1A. This article is accompanied by an editorial on p. 5. 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 an audio podcast. This article has a visual abstract available in the online version. J.-J.P. and J.-L.H. contributed equally to this article.

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history of the patient.[6] Hip and knee surgery are the most common intermediate-risk surgeries in the United States,[7] and current projections estimate that the incidence of these surgeries will increase dramatically by 2030.[8] Therefore, the Agency for Healthcare Research and Quality (Rockville, Maryland), together with the American College of Surgeons (Chicago, Illinois) and the Johns Hopkins Medicine Armstrong Institute for Patient Safety Quality (Baltimore, Maryland), has created the Safety Program for Improving Surgical Care and Recovery, especially for knee and hip arthroplasty.[9,10] This program concluded that intraoperative fluid management should aim to minimize fluids and maintain euvolemia.[9,10]

The noninvasive "plug and play" sensor (Masimo Corporation, USA) that uses the pleth variability index was developed to assess fluid responsiveness using plethysmographic variations induced by mechanical ventilation and thus achieve euvolemia during surgery. Encouraging results have been published for this new technology,[11,12] but the clinical benefits of this device for intermediate-risk surgery remain uncertain.

In this context, the aim of the present multicenter, randomized study was to compare a strategy using individualized preload monitoring with the pleth variability index with that for a control group using noninvasive blood pressure monitoring for intermediate-risk surgical patients scheduled for elective orthopedic surgery. We tested the primary hypothesis that pleth variability index-guided fluid management reduces hospital length of stay. Secondarily, we tested the hypothesis that pleth variability index guidance reduces postoperative morbidity.

## Materials and Methods

### Study Design

The hemodynamic Optimization using the Pleth Variability Index (OPVI) trial was an investigator-initiated, randomized, stratified, parallel-group, nonblinded, clinical trial conducted in five French university and nonuniversity hospitals. The main hypothesis was analyzed with respect to the superiority of pleth variability index to decrease the length of stay in comparison with that of the control group. The study protocol was approved for all centers on May 23, 2014, by the official ethics committee of the University Hospital of Caen (Ethical Committee North West 3, Caen University Hospital, Caen, France)[13] and recorded at clinicaltrials.gov on August 4, 2014 (NCT02207296, Principal Investigator M.-O. Fischer). Written informed consent was obtained before each patient was randomized and had surgery. The study protocol and the statistical analysis plan have been previously published[14] and are available in Supplemental Digital Content 1 (http://links.lww.com/ALN/C329). An independent data and safety monitoring committee oversaw the study and reviewed the blinded safety data.

The included patients were considered intermediate risk after accounting for the surgical procedure (hip or knee arthroplasty was considered intermediate-risk surgery)[5] and the medical history of each patient (which was considered a low-to-intermediate risk if the cardiac risk factor was under 3).[6] Patients aged 18 yr or older, in sinus rhythm and scheduled for a planned hip or knee arthroplasty with general anesthesia were eligible for recruitment. Participants were recruited into the study after being approached by study staff. The exclusion criteria were as follows: refused to provide consent, was pregnant, had cardiac arrhythmia, had sepsis, had chronic kidney disease with dialysis, had dark-colored skin (owing to limitations of the plethysmography technology), or were under judicial protection. Patients at high risk for surgery based on their medical history and who were recommended to have a cardiac output monitor and/or an arterial line were not included in the study.

Eligible patients were assigned in a 1:1 ratio to either a standard or individualized treatment strategy. The intervention period started with the induction of anesthesia and continued until discharge from the postanesthesia care unit (PACU).

### All Patients

Each patient underwent the usual monitoring (including vital sign monitoring, noninvasive blood pressure monitoring, and pulse oximetry monitoring), and all recommendations to prevent complications were applied.[15,16] The pleth variability index forehead sensor (LNOP TF-I, Masimo Corporation) was connected to a dedicated monitor (Radical 7, Masimo Corporation) for all study participants, but the monitor was blinded to the investigators in the control group. For all patients, all hemodynamic data were registered and analyzed offline. The use of additional regional anesthesia, choice of anesthetic drugs, and operative pain management were at the discretion of the attending anesthesiologist. The investigators indicated that the ventilator patterns should be strictly as follows: controlled ventilation with a tidal volume of 8 ml/kg of ideal body weight; a respiratory rate and fraction of inspired oxygen between 35 and 45 mmHg, according to a range of end tide carbon dioxide; and a pulse oxygen saturation greater than 96%. Lactated Ringer solution was intravenously infused at a rate of 3 ml · $kg^{-1}$ · $h^{-1}$ to satisfactorily maintain hydration.

### Pleth Variability Index Group

The patients in the intervention group first received fluids according to their pleth variability index values, followed by vasopressors according to a hemodynamic algorithm (Supplemental Digital Content 1, http://links.lww.com/ALN/C329). The algorithm was developed for the OPVI study by an expert group and was designed to be run in the operating room by both medical and nursing staff. The pleth variability index monitor was used from the initiation of mechanical ventilation after general anesthesia induction until the end of surgery. This noninvasive technology has

been used in clinical practice for more than 10 yr.[11] Because the forehead sensor has been shown to be more accurate in predicting fluid responsiveness than digital sensors, the forehead sensor was exclusively used in the present study.[17] The use of this hemodynamic therapy algorithm was supported by high-quality clinical studies, and the algorithm has an excellent cardiovascular safety profile.[4,18] Intravenous gelatin solution (Gelofusine 4%; B-Braun Medical, Germany) was administered in individualized 3-ml/kg boluses to increase and maintain the pleth variability index value above 13%, which was previously described as a valuable cutoff value.[17] After this first step, vasopressors were administered to maintain the mean arterial pressure above 65 mmHg, along with up to 30 mg of ephedrine followed by norepinephrine at low doses according to a simple protocol (Supplemental Digital Content 2, http://links.lww.com/ALN/C330).

### Control Group

In the control group, the patients received either fluid loading or vasopressors at the discretion of the attending anesthesiologist to maintain the mean arterial pressure above 65 mmHg (Supplemental Digital Content 1, http://links.lww.com/ALN/C329). After 30 mg of ephedrine, a low dose of norepinephrine was recommended by a simple protocol (Supplemental Digital Content 2, http://links.lww.com/ALN/C330). Although a pleth variability index was connected and registered, the device was blinded to the clinical staff, and the data were retrospectively used offline.

### Study Outcomes

The primary outcome was the postoperative hospital length of stay in days using the real data. The predefined secondary outcomes included the theoretical hospital length of stay in days using a specified checklist completed every 12 h by research staff, serious postoperative cardiac complications (at least one of the following: cardiac arrest, arrhythmia, or heart failure requiring treatment), acute postoperative renal failure (defined as an increase in creatinine concentration of at least 30% compared with the preoperative value), postoperative troponin Ic measured on days 1 and 3 postoperatively, and arterial lactate measurements in the PACU. The primary outcome, initially defined in 2014 as the theoretical hospital length of stay, was changed during 2015 to the real postoperative hospital length of stay,[14] which is a more pragmatic and robust criterion in real life.

### Randomization and Blinding

Enrollment, randomization (1:1 allocation ratio), and data collection were performed using a dedicated and secure web-based system. Blocked randomization was performed after stratifying the patients according to the center and type of surgery (hip or knee arthroplasty) before surgery.

The allocation sequence was generated by the principal statistician; anesthesiologists evaluated eligibility, obtained informed written consent and assigned participants to study groups. Although anesthesiology staff members could not be blinded to the group assignments, strict blinding of the patients, surgeons, statistician, and the data and safety monitoring committee was maintained during the operative period and postoperative care (PACU and surgical ward). Patients in each group remained indistinguishable because the material used in the pleth variability index group and control group was similar and blinded to both patients and surgeons. The surgeons were the postoperative care providers and chose the discharge day while remaining completely blinded to the group allocation, as were the statistician and data and safety monitoring committee, who used an anonymous database.

### Statistical Analysis

Assuming a two-sided $\alpha$ risk of 5% and a power of 80%, we computed that the sample size should be 193 patients per group to detect a 1-day difference in the primary outcome (postoperative hospital length of stay), assuming a SD of 3.5 days (using the French national database). Therefore, we planned to include 440 patients.

We tested the hypothesis that pleth variability index would reduce the length of stay as compared with the standard of care. Although our hypothesis was one-sided, we used two-sided tests for all comparisons.

Categorical variables were described as percentages, and continuous variables were described as the mean ± SD or median (interquartile range), as appropriate. The primary outcome analysis followed the modified intention-to-treat principle, which recommends that all randomized patients be analyzed in their assigned group. For the primary outcome, we created a linear regression model of the primary outcome, including the randomization groups and stratification factors (center and type of surgery), as appropriate. The primary outcome data were tested for normality by the Kolmogorov–Smirnov test, and this assumption was met. Categorical variables were compared between groups using Fisher exact tests or Pearson chi-square tests for heterogeneity. Continuous variables were compared between groups with a *t* test for independent samples or Wilcoxon rank tests, as appropriate. We conducted a sensitivity analysis in the pure intent-to-treat population among all randomized patients with multiple imputations (five data sets) using a multivariate normal distribution. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, USA). A *P* value less than 0.05 was considered statistically significant.

## Results

### Study Population

During the study period from March 11, 2015, to March 16, 2017, a total of 1,820 patients were screened for eligibility,

447 were randomized, and 438 were included in the primary outcome analysis: 216 were allocated to the pleth variability index group, and 222 were allocated to the control group (fig. 1). The baseline patient characteristics were similar between the groups (table 1).

## Pleth Variability Index and Intraoperative Management

Pleth variability index monitoring was implemented for all patients, and the pleth variability index data were recorded for 196 (91%) patients in the pleth variability index group and 190 (86%) patients in the control group. Throughout the recording, the mean ± SD pleth variability index was 15.7 ± 5.7% in the individualized treatment group and 15.6 ± 5.3% in the control group ($P = 0.898$). The mean ± SD percentage of time that the pleth variability index was less than 13% was 36 ± 31% of the total recording time for the pleth variability index group *versus* 31 ± 30% for the control group ($P = 0.223$; Supplemental Digital Content 3, http://links.lww.com/ALN/C331). The perioperative hemodynamic data are presented in table 2. Fluid loading was used more often in the pleth variability index group (178 of 210 [85%] patients) than in the control group (77 of 211 [36%] patients; $P < 0.001$). Among all patients, the cumulative volume of fluid infused throughout the surgery was significantly larger in the pleth variability index group than in the control group (1,088 ± 606 ml *vs.* 677 ± 608 ml; $P < 0.001$). Vasopressors were used for 114 (54%) patients in the pleth variability index group and for 125 (59%) patients in the control group ($P = 0.326$). The most common vasopressor used was ephedrine (n = 231), with similar doses used between the pleth variability index group and the control group (16.9 ± 8.5 mg *vs.* 17.1 ± 9.0 mg; $P = 0.810$); norepinephrine was used for 9 (4%) patients in each group (table 2 and fig. 2).

## Outcomes

The real hospital length of stay was 6 ± 3 days for the pleth variability index group (n = 216) and 6 ± 3 days for the control group (n = 222; adjusted difference, 0.0 day; 95% CI, −0.6 to 0.5; $P = 0.860$; fig. 3). This result was consistent with the multiple imputation sensitivity analysis (adjusted difference, 0.0 day; 95% CI, −0.6 to 0.5; $P = 0.786$).

The secondary objectives and the complications are detailed in table 3. The theoretical hospital length of stay for

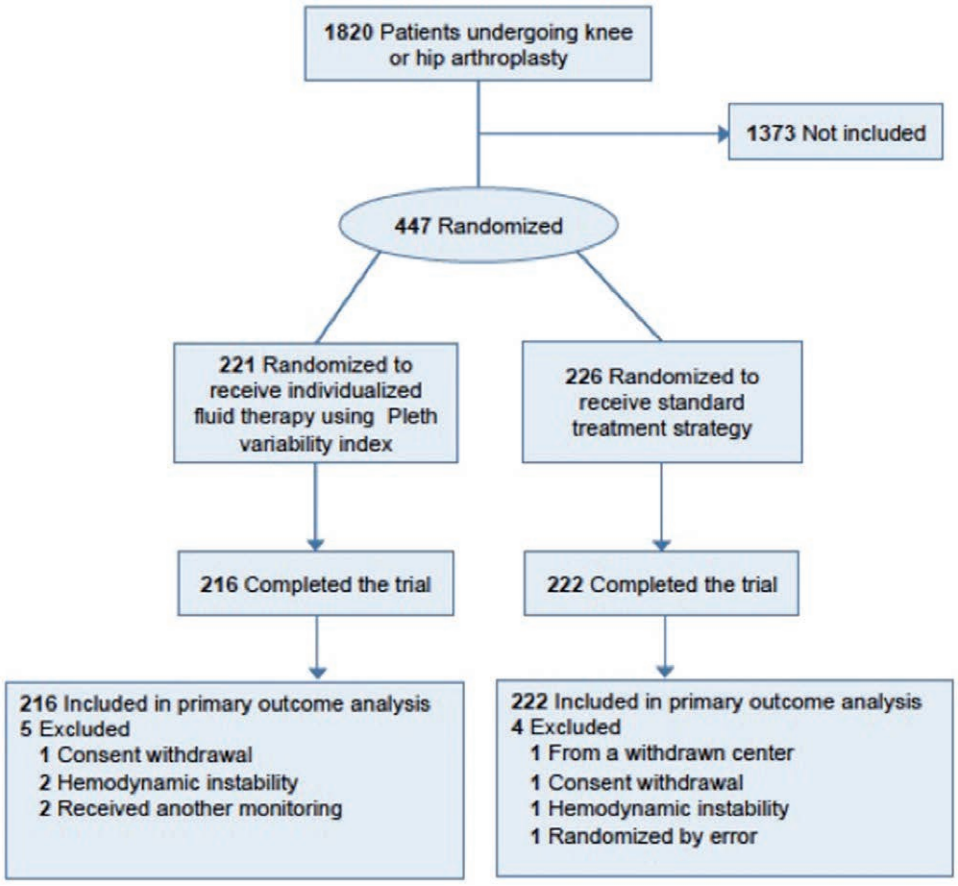


**Fig. 1.** Flowchart of the participant enrollment process throughout the study.

**Table 1.** Demographics and Baseline Characteristics

| Characteristics | Pleth Variability Index Group (n = 216) | Control Group (n = 222) |
|---|---|---|
| Age, yr | 65 ± 10 | 66 ± 10 |
| Sex, | | |
| Male | 79 (37) | 82 (37) |
| Female | 137 (63) | 140 (63) |
| Body mass index, kg/m² | 29 ± 6 | 30 ± 6 |
| Creatinine, mean ± SD, µmol/l | 70 ± 16 | 74 ± 23 |
| ASA Physical Status | | |
| I | 36 (17) | 30 (14) |
| II | 149 (69) | 152 (68) |
| III | 28 (13) | 39 (18) |
| IV | 0 (0) | 0 (0) |
| V | 0 (0) | 0 (0) |
| Lee score | | |
| 0 | 199 (92) | 193 (87) |
| 1 | 14 (7) | 25 (11) |
| 2 | 2 (1) | 4 (2) |
| 3 | 0 (0) | 0 (0) |
| 4 | 1 (1) | 0 (0) |
| 5 | 0 (0) | 0 (0) |
| Comorbidities | | |
| Total | 162 (75) | 184 (83) |
| Smoking | 43 (20) | 40 (18) |
| Diabetes | 25 (11) | 36 (16) |
| Dyslipidemia | 70 (32) | 71 (32) |
| Hypertension | 105 (48) | 128 (57) |
| Arteritis | 4 (2) | 6 (3) |
| Heart disease | 13 (6) | 18 (8) |
| Renal insufficiency | 1 (0) | 8 (4) |
| Hepatic insufficiency | 1 (0) | 3 (1) |
| Cirrhosis | 1 (0) | 2 (1) |
| Respiratory disease | 34 (16) | 39 (17) |
| Asthma | 12 (5) | 14 (6) |
| COPD | 7 (3) | 9 (4) |
| Neoplasia | 23 (11) | 21 (9) |
| Type of surgery | | |
| Hip arthroplasty | 122 (56) | 129 (58) |
| Knee arthroplasty | 94 (44) | 93 (42) |
| First surgery | 188 (87) | 196 (88) |
| Reoperation | 28 (13) | 26 (12) |
| Hypnotics | 210 (97) | 212 (95) |
| Propofol | 203 (94) | 210 (95) |
| Median [IQR], mg | 200 [200–295] | 200 [160–300] |
| Ketamine | 172 (80) | 179 (81) |
| Median [IQR], mg | 20 [20–30] | 20 [20–30] |
| Midazolam | 98 (45) | 94 (42) |
| Median [IQR], mg | 1 [1–2] | 1 [1–2] |
| Halogenated gas | 157 (73) | 160 (72) |
| Median inhaled fraction [IQR], % | 3 [2–5] | 3 [2–5] |
| Opioid agents | 205 (95) | 206 (93) |
| Remifentanil | 11 (5) | 14 (6) |
| Median dose [IQR], ng | 454.5 [334–670] | 398.5 [315–468] |
| Sufentanil | 194 (90) | 192 (86) |
| Median dose [IQR], µg | 30 [20–35] | 30 [20–35] |
| Neuromuscular blockade agent | 87 (40) | 87 (39) |
| Median dose (IQR), mg | 30 [20–35] | 30 [10–40] |

The data are represented as N (%), means ± SD, or median [25th, 75th percentiles].
ASA, American Society of Anesthesiologists Physical Status classification system; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

**Table 2.** Hemodynamic Data

| | Pleth Variability Index Group (n = 216) | Control Group (n = 222) |
|---|---|---|
| Heart rate, beats/min | 65 ± 10 | 64 ± 10 |
| MAP, mmHg | 82 ± 10 | 81 ± 11 |
| MAP < 65 mmHg | | |
| Duration, min | 8 [0–80] | 6 [0–30] |
| Percentage of recording time, % | 8 [0–70] | 7 [0–92] |
| MAP < 55 mmHg | | |
| Duration, min | 0 [0–150] | 0 [0–30] |
| Percentage of recording time, % | 0 [0–100] | 0 [0–28] |
| MAP/heart rate ratio | 1.3 ± 0.2 | 1.3 ± 0.2 |
| Fluid administration | | |
| Gelatin | 178 (85) | 77 (36) |
| Volume of gelatin | 683 ± 452 | 427 ± 250 |
| Total IV fluid loading | 1,088 ± 606 | 677 ± 608 |
| Transfusion | 3 (1) | 2 (1) |
| Vasopressor and inotrope use | 114 (54) | 125 (59) |
| Ephedrine | 112 (52) | 122 (55) |
| Norepinephrine | 9 (4) | 9 (4) |
| Dobutamine | 0 (0) | 1 (0) |

Data are represented as N (%), mean ± SD, or median [25th, 75th percentiles].
IV, intravenous; MAP, mean arterial pressure.

the pleth variability index group and control group were 4 ± 2 and 4 ± 1 days, respectively ($P$ = 0.238). Serious postoperative cardiac complications occurred in 3 (1%) and 2 (1%) patients in the pleth variability index and control groups, respectively ($P$ = 0.681). Acute postoperative renal failure occurred in 9 of 216 (4%) patients and 8 of 222 (4%) patients in the pleth variability index and control groups, respectively ($P$ = 0.808). The postoperative troponin Ic concentration was elevated for 6 of 216 (3%) patients in the pleth variability index group and 5 of 222 (2%) patients in the control group ($P$ = 0.768). No significant difference was observed between the two groups in the arterial lactate measurements taken in the PACU (1.44 ± 1.01 mmol/l in the pleth variability index group *vs.* 1.43 ± 0.95 mmol/l in control group; $P$ = 0.974). The adverse events alleviated by the safety committee from inclusion to day 30 are reported in Supplemental Digital Content 4 (http://links.lww.com/ALN/C332).

## Discussion

In this multicenter, randomized, stratified clinical trial involving intermediate-risk surgical patients having elective orthopedic surgery with general anesthesia, an individualized goal-directed hemodynamic strategy using pleth variability index increased the amount of fluid loading compared with that yielded by standard management strategies but did not provide any clinical benefits in terms of hospital length of stay, serious cardiac events, renal failure, or postoperative lactate or troponin Ic concentrations.

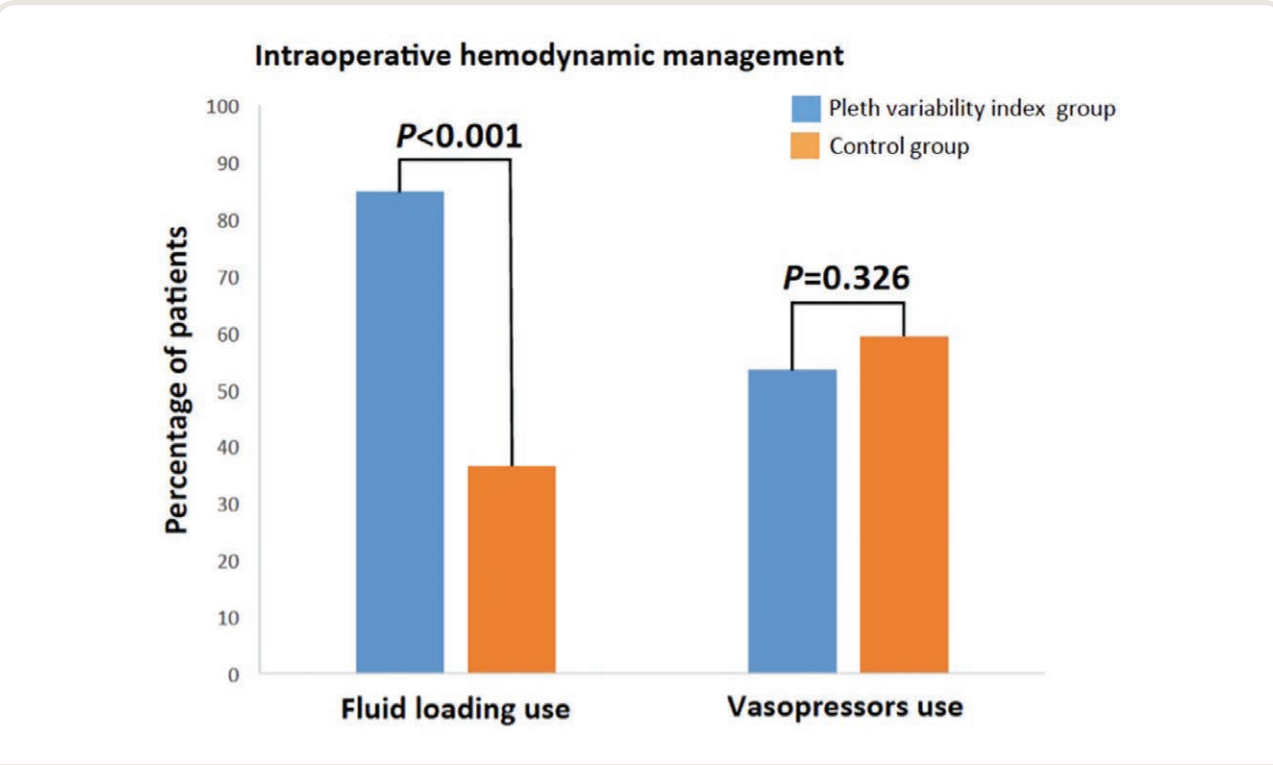


**Fig. 2.** Use of fluid loading and vasopressors in the pleth variability index and control groups. Fluid loading was used more frequently in the pleth variability index group (*blue*) than in the control group (*orange*; $P < 0.001$), whereas vasopressor use was similar between the two groups ($P = 0.326$). The data are expressed as percentages.

The OPVI trial was an academic multicenter randomized study designed to assess the clinical impact of individualized hemodynamic strategies for intermediate-risk surgical patients. Although this population represents the majority of patients who have planned surgery worldwide, most studies have selected high-risk patients for postoperative morbidity and mortality. This selection bias decreases the external validity of studies that investigate high-risk patients and reinforces the need for further studies with patients considered intermediate risk for surgery based on the type of surgery or intermediate risk for comorbidities using the American Society of Anesthesiologists (ASA) Physical Status classification system.[5,19] In the present study, the patient population preoperatively showed a low ASA classification[19] and a low Lee score,[6] in accordance with an intermediate-risk score; hip and knee arthroplasties are classified as intermediate-risk surgeries.[5]

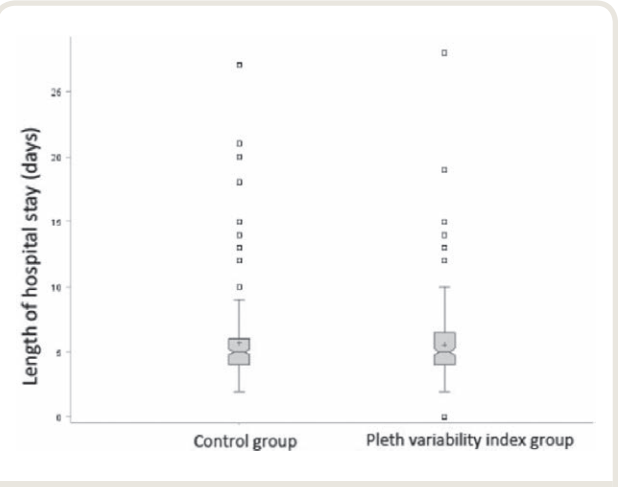


**Fig. 3.** Real hospital length of stay for the pleth variability index and control groups. Real hospital length of stay is expressed as the median; the *top* and *bottom borders* of the *box* are the 25th and 75th percentiles, respectively; the *whiskers* are 1.5 times the interquartile range; and the *squares* represent the extreme outliers.

There is evidence for the benefit of perioperative goal-directed therapy, but its adoption into clinical practice has been slow. One explanation for the poor use of such therapy at the bedside could be the invasiveness and difficulties in using hemodynamic monitoring.[20,21] Some studies have evaluated the use of a noninvasive pleth variability index for goal-directed hemodynamic therapy during high-risk surgery with encouraging results. Two randomized studies showed that pleth variability index–guided fluid therapy could decrease fluid administration and postoperative lactate concentration after major abdominal surgery.[12,22] Compared with esophageal Doppler or pulse pressure

**Table 3.** Secondary Objectives and Complications

| | Pleth Variability Index Group (n = 216) | Control Group (n = 222) |
|---|---|---|
| Theoretical length of hospital stay, days | 4.1 ± 2.3 | 3.8 ± 1.4 |
| Number of perioperative complications | | |
| 0 complications | 188 (87) | 192 (86) |
| 1 complication | 19 (9) | 22 (10) |
| 2 complications | 3 (1) | 1 (0) |
| 3 complications | 0 (0) | 2 (1) |
| 4 complications | 1 (0) | 0 (0) |
| No data | 5 (2) | 5 (2) |
| Serious perioperative cardiac complications | 3 (1) | 2 (1) |
| Cardiac arrhythmia requiring treatment | 1 (0) | 0 (0) |
| Acute lung edema | 0 (0) | 0 (0) |
| Cardiac death | 0 (0) | 0 (0) |
| Other cardiac complication | 2 (1) | 2 (1) |
| Postoperative troponin Ic elevation (> 0.06 µg/l) | 6 (3) | 5 (2) |
| Perioperative noncardiac complications | 23 (11) | 21 (10) |
| Noncardiac death | 0 (0) | 0 (0) |
| Respiratory distress (noninvasive ventilation or intubation) | 1 (0) | 0 (0) |
| Stroke | 0 (0) | 0 (0) |
| Intensive care unit hospitalization | 0 (0) | 0 (0) |
| Postoperative ileus > 4 days | 0 (0) | 0 (0) |
| Postoperative infections | 1 (0) | 2 (1) |
| Acute kidney failure | 9 (4) | 8 (4) |
| Other noncardiac complications | 21 (10) | 18 (8) |
| Postoperative arterial lactate, mmol/l | 1.4 ± 1.0 | 1.4 ± 0.9 |

The data are represented as N (%) or means ± SD.

variations, goal-directed fluid therapy using the pleth variability index appears to be an acceptable alternative with regard to postoperative complications after major abdominal surgery.[23,24] Compared with the standard strategy without hemodynamic monitoring, the use of the pleth variability index could decrease fluid loading for obese patients having laparoscopic bariatric surgery.[25] However, no study has focused on hospital length of stay or low-to-intermediate–risk surgery, such as orthopedic surgery, which are actually the most common types of surgeries.[8]

In the present OPVI trial, the enrollment process and use of the pleth variability index were satisfactory in terms of the following: (1) pleth variability index data were recorded for the majority of patients, and (2) the high fluid loading for the pleth variability index group, in contrast with that of the control group, suggested at the protocol was correctly followed at the bedside. However, the pleth variability index did not decrease the hospital length of stay or the postoperative morbidity compared with the standard strategy. Some explanations exist for these results. First, this result could be related to the fact that the study population did not benefit from using the hemodynamic algorithm through dedicated monitoring, as suggested by the absence of differences in the incidence of serious cardiac complications or renal failure and postoperative lactate or troponin Ic concentration between the two groups. Alternatively, the pleth variability index may not be reliable enough to allow effective hemodynamic optimization in a surgical setting. However, patients with regular sinus rhythm under mechanical ventilation without spontaneous breathing could use this dynamic index;[11] in addition, we used forehead sensors that have been shown to decrease the background noise described with digital sensors.[17] Indeed, the vasomotor tone and vasopressor have been previously reported to markedly alter the accuracy of pleth variability index measurements at the digital site.[26]

This trial has several limitations. In the pleth variability index group, the pleth variability index was less than 13% for nearly one third of the total duration of recording, which might suggest that the investigators did not follow the protocol. In fact, the study protocol was carefully applied by a staff member for each inclusion. Some technical explanations may be discussed: the length of time that the pleth variability index was available (approximately 80% of the recording time; Supplemental Digital Content 3, http://links.lww.com/ALN/C331); the remaining time (decreased by the average over a 2-min period) to the pleth variability index calculation for each intermittent signal during surgery; and the sensitivity of the pleth variability index itself. The median pleth variability index value in the interventional group was just above the threshold value of 13%. Moreover, a recent meta-analysis found high variability regarding the best threshold for pleth variability index values, ranging from 7 to 20%.[27] One reason for the high variability might be the different settings in which the studies have been conducted (the reliability of the pleth variability index was limited in the operating room in comparison with the intensive care unit). Another reason might be that the pleth variability index is highly affected by external conditions such as low cardiac output, hypothermia, use of vasoactive drugs, and peripheral vascular disease. The question around the threshold pleth variability index value emphasizes the importance of precisely setting the device according to the clinical situation. A gray zone approach could partially explain why patients in the pleth variability index group received more than the control group fluids but had the same need for vasopressors. A dynamic view of dynamic indices has been suggested as an alternative to minimize the problems surrounding the threshold value, but hemodynamic maneuvers (mini-fluid challenge, tidal volume challenge, or alveolar recruitment maneuver) complicate the use of a simple tool and are possibly not usable in the clinical setting.[27]

Second, even though the attending anesthesiologist was aware of the group allocations, the surgeons who were responsible for patient discharge (primary outcome) were not. Third, we cannot conclude whether the absence of differences was related to the failure of pleth variability index monitoring to optimize the volemia or was related to the

therapeutic strategy. Reference cardiac output monitoring or arterial monitoring with pulse pressure variations data could answer this question, but the use of invasive devices such as thermodilution with a pulmonary arterial catheter or arterial line for intermediate-risk surgical patients was considered unethical. However, the absence of differences in the secondary objectives and adverse events point toward the absence of efficacy from the individualized hemodynamic strategy for intermediate-risk surgical patients in the present study. If we power a trial based on the 10% observed complication rate, for 20% reduction and a power of 80%, more than 6,000 patients are mandatory to show a difference.

Finally, this study was conducted with orthopedic surgeries. Although these procedures represent the most frequently performed surgeries in the United States, our results may not be generalizable to other types of surgery.

## Conclusions

Among patients having intermediate-risk orthopedic surgery with general anesthesia, an individualized goal-directed hemodynamic strategy using the pleth variability index did not provide any benefits compared with a standard management strategy. Large randomized controlled studies are mandatory to precisely determine the place of the pleth variability index in anesthesia practice.

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## Competing Interests

The authors declare no competing interests.

## Reproducible Science

Full protocol available at: marcolivierfischer@yahoo.fr. Raw data available at: parienti-jj@chu-caen.fr.

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## References

1. Pearse RM, Moreno RP, Bauer P, Pelosi P, Metnitz P, Spies C, Vallet B, Vincent JL, Hoeft A, Rhodes A; European Surgical Outcomes Study (EuSOS) group for the Trials groups of the European Society of Intensive Care Medicine and the European Society of Anaesthesiology: Mortality after surgery in Europe: A 7 day cohort study. Lancet 2012; 380:1059–65
2. Rose J, Weiser TG, Hider P, Wilson L, Gruen RL, Bickler SW: Estimated need for surgery worldwide based on prevalence of diseases: A modelling strategy for the WHO Global Health Estimate. Lancet Glob Health 2015; 3:S13–20
3. International Surgical Outcomes Study group: Global patient outcomes after elective surgery: Prospective cohort study in 27 low-, middle- and high-income countries. Br J Anaesth 2016; 117:601–9
4. Pearse RM, Harrison DA, MacDonald N, Gillies MA, Blunt M, Ackland G, Grocott MP, Ahern A, Griggs K, Scott R, Hinds C, Rowan K; OPTIMISE Study Group: Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: A randomized clinical trial and systematic review. JAMA 2014; 311:2181–90
5. Kristensen SD, Knuuti J, Saraste A, Anker S, Bøtker HE, De Hert S, Ford I, Gonzalez Juanatey JR, Gorenek B, Heyndrickx GR, Hoeft A, Huber K, Iung B, Kjeldsen KP, Longrois D, Luescher TF, Pierard L, Pocock S, Price S, Roffi M, Sirnes PA, Uva MS, Voudris V, Funck-Brentano C; Authors/Task Force Members: 2014 ESC/ESA Guidelines on non-cardiac surgery: Cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: Cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur J Anaesthesiol 2014; 31:517–73
6. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, Ludwig LE, Pedan A, Goldman L: Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999; 100:1043–9
7. McDermott KW, Freeman WJ, Elixhauser A: Overview of Operating Room Procedures during Inpatient Stays in U.S. Hospitals, 2014: Statistical Brief #233, Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville (M.D.), Agency for Healthcare Research and Quality (US), 2006
8. Kurtz S, Ong K, Lau E, Mowat F, Halpern M: Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007; 89:780–5
9. Soffin EM, Gibbons MM, Ko CY, Kates SL, Wick EC, Cannesson M, Scott MJ, Wu CL: Evidence review conducted for the Agency for Healthcare Research and Quality Safety Program for Improving Surgical Care and Recovery: Focus on anesthesiology for total hip arthroplasty. Anesth Analg 2019; 128:454–65
10. Soffin EM, Gibbons MM, Ko CY, Kates SL, Wick E, Cannesson M, Scott MJ, Wu CL: Evidence review conducted for the Agency for Healthcare Research and

Quality Safety Program for Improving Surgical Care and Recovery: Focus on anesthesiology for total knee arthroplasty. Anesth Analg 2019; 128:441–53
11. Cannesson M, Desebbe O, Rosamel P, Delannoy B, Robin J, Bastien O, Lehot JJ: Pleth variability index to monitor the respiratory variations in the pulse oximeter plethysmographic waveform amplitude and predict fluid responsiveness in the operating theatre. Br J Anaesth 2008; 101:200–6
12. Forget P, Lois F, de Kock M: Goal-directed fluid management based on the pulse oximeter-derived pleth variability index reduces lactate levels and improves fluid management. Anesth Analg 2010; 111:910–4
13. Toulouse E, Masseguin C, Lafont B, McGurk G, Harbonn A, A Roberts J, Granier S, Dupeyron A, Bazin JE: French legal approach to clinical research. Anaesth Crit Care Pain Med 2018; 37:607–14
14. Fischer MO, Daccache G, Lemoine S, Tavernier B, Compère V, Hulet C, Bouchakour CE, Canevet C, Gérard JL, Guittet L, Lorne E, Hanouz JL, Parienti JJ: The OPVI trial: Perioperative hemodynamic optimization using the plethysmographic variability index in orthopedic surgery: Study protocol for a multicenter randomized controlled trial. Trials 2015; 16:503
15. Risk Management Analysis Committee of the French Society for Anesthesia and Critical Care (SFAR), French Society for Clinical Pharmacy (SFPC): Preventing medication errors in anesthesia and critical care (abbreviated version). Anaesth Crit Care Pain Med 2017; 36:253–8
16. French Society for Anaesthesia and Intensive Care (SFAR), French Ophthalmology Society (SFO), French-speaking Intensive Care Society (SRLF), Keita H, Devys JM, Ripart J, Frost M, Cochereau I, Boutin F, Guerin C, Fletcher D, Compere V: Eye protection in anaesthesia and intensive care. Anaesth Crit Care Pain Med 2017; 36:411–8
17. Fischer MO, Pellissier A, Saplacan V, Gérard JL, Hanouz JL, Fellahi JL: Cephalic *versus* digital plethysmographic variability index measurement: A comparative pilot study in cardiac surgery patients. J Cardiothorac Vasc Anesth 2014; 28:1510–5
18. Benes J, Giglio M, Brienza N, Michard F: The effects of goal-directed fluid therapy based on dynamic parameters on post-surgical outcome: A meta-analysis of randomized controlled trials. Crit Care 2014; 18:584
19. American Society of Anesthesiologists: ASA Physical Status Classification System. Available at: https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system. Accessed March 5, 2014.
20. Kaufmann T, Saugel B, Scheeren TWL: Perioperative goal-directed therapy: What is the evidence? Best Pract Res Clin Anaesthesiol 2019; 33:179–87
21. Yu Y, Dong J, Xu Z, Shen H, Zheng J: Pleth variability index-directed fluid management in abdominal surgery under combined general and epidural anesthesia. J Clin Monit Comput 2015; 29:47–52
22. Bahlmann H, Hahn RG, Nilsson L: Pleth variability index or stroke volume optimization during open abdominal surgery: A randomized controlled trial. BMC Anesthesiol 2018; 18:115
23. Coeckelenbergh S, Delaporte A, Ghoundiwal D, Bidgoli J, Fils JF, Schmartz D, Van der Linden P: Pleth variability index *versus* pulse pressure variation for intraoperative goal-directed fluid therapy in patients undergoing low-to-moderate risk abdominal surgery: A randomized controlled trial. BMC Anesthesiol 2019; 19:34
24. Demirel İ, Bolat E, Altun AY, Özdemir M, Beştaş A: Efficacy of goal-directed fluid therapy via pleth variability index during laparoscopic Roux-en-Y gastric bypass surgery in morbidly obese patients. Obes Surg 2018; 28:358–63
25. Landsverk SA, Hoiseth LO, Kvandal P, Hisdal J, Skare O, Kirkeboen KA: Poor agreement between respiratory variations in pulse oximetry photoplethysmographic waveform amplitude and pulse pressure in intensive care unit patients. Anesthesiology 2008; 109:849–55
26. Liu T, Xu C, Wang M, Niu Z, Qi D: Reliability of pleth variability index in predicting preload responsiveness of mechanically ventilated patients under various conditions: A systematic review and meta-analysis. BMC Anesthesiol 2019; 19:67
27. Fischer MO, Guinot PG, Biais M, Mahjoub Y, Mallat J, Lorne E; French Hemodynamic Team (FHT): A dynamic view of dynamic indices. Minerva Anestesiol 2016; 82:1115–21

## Appendix 1. The OPVI Trial Group

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## ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

# The Surgeon As "Swindler": A Corny Use of Chloroform


Hidden in the Wood Library-Museum Archives is this bifold sheet (*top left*) containing three autograph pages of "Riddles from Miss C. Corbet" of Adderley, England. Dated "Jan$^{y}$ 10$^{th}$ / 56" (1856, *top right*), there are 19 riddles in all. The riddler was 20-year-old Clara Anna Corbet (1835 to 1916), the fourth of eight children born to soon-to-be Rector Richard Corbet and his wife Eleanor. In one instance, Clara likened "a surgeon using Chloroform," who "cuts away without…pain," to "a swindler," who "cuts away without paying" (*bottom*). Miss Corbet, however, offered no chloroform to palliate the pain of reading her riddle. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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