

A Randomized Trial of Continuous Noninvasive Blood Pressure Monitoring During Noncardiac Surgery

Kamal Maheshwari, MD, MPH,*† Sandeep Khanna, MD,† Gausan Ratna Bajracharya, MD,* Natalya Makarova, MS,‡ Quinton Riter, BS,* Syed Raza, BS,* Jacek B. Cywinski, MD,† Maged Argalious, MD, MBA, MEd, FASE,† Andrea Kurz, MD,*† and Daniel I. Sessler, MD*

BACKGROUND: Intraoperative hypotension is associated with postoperative mortality. Early detection of hypotension by continuous hemodynamic monitoring might prompt timely therapy, thereby reducing intraoperative hypotension. We tested the hypothesis that continuous noninvasive blood pressure monitoring reduces intraoperative hypotension.

METHODS: Patients ≥ 45 years old with American Society of Anesthesiologists physical status III or IV having moderate-to-high-risk noncardiac surgery with general anesthesia were included. All participating patients had continuous noninvasive hemodynamic monitoring using a finger cuff (ClearSight, Edwards Lifesciences, Irvine, CA) and a standard oscillometric cuff. In half the patients, randomly assigned, clinicians were blinded to the continuous values, whereas the others (unblinded) had access to continuous blood pressure readings. Continuous pressures in both groups were used for analysis. Time-weighted average for mean arterial pressure < 65 mm Hg was compared using 2-sample Wilcoxon rank-sum tests and Hodges Lehmann estimation of location shift with corresponding asymptotic 95% CI.

RESULTS: Among 320 randomized patients, 316 were included in the intention-to-treat analysis. With 158 patients in each group, those assigned to continuous blood pressure monitoring had significantly lower time-weighted average mean arterial pressure < 65 mm Hg, 0.05 [0.00, 0.22] mm Hg, versus intermittent blood pressure monitoring, 0.11 [0.00, 0.54] mm Hg ($P = .039$, significance criteria $P < .048$).

CONCLUSIONS: Continuous noninvasive hemodynamic monitoring nearly halved the amount of intraoperative hypotension. Hypotension reduction with continuous monitoring, while statistically significant, is currently of uncertain clinical importance. (Anesth Analg 2018;127:424–31)

KEY POINTS

- **Question:** Does continuous noninvasive blood pressure monitoring reduce intraoperative hypotension?
- **Findings:** Patients assigned to continuous blood pressure monitoring had significantly lower time-weighted average mean arterial pressure < 65 mm Hg, 0.05 [0.00, 0.22] mm Hg, versus intermittent blood pressure monitoring, 0.11 [0.00, 0.54] mm Hg ($P = .039$).
- **Meaning:** Continuous noninvasive hemodynamic monitoring nearly halved the amount of intraoperative hypotension.

Intraoperative hypotension is strongly associated with postoperative mortality. For example, hypotension was the most important factor responsible for postoperative mortality in the Perioperative Ischemia Evaluation Trial.¹ Many other studies similarly report strong associations between hypotension and postoperative acute kidney injury (AKI) and myocardial injury, possibly due to ischemia-reperfusion or supply-demand mismatch.^{1–6} To the extent that these associations are

causal, optimizing intraoperative hemodynamics and avoiding hypotension may reduce perioperative myocardial and renal injury. A causal relationship is supported by a recent randomized trial in which controlling systolic pressure to within 10% of baseline values reduced postoperative organ dysfunction.⁷ Intraoperative hypotension has various definitions,⁸ but mean arterial pressure (MAP) < 65 mm Hg has been associated with worse outcomes in several analyses.^{4,9,10}

From the Departments of *Outcomes Research, †General Anesthesiology, and ‡Quantitative Health Sciences and Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland, Ohio.

Accepted for publication April 19, 2018.

Funding: This study was supported by an Investigator Initiated Study grant from Edwards Lifesciences. The Department of Outcomes Research has research contracts with Edwards Lifesciences. These financial interests are within permissible limits established by the Cleveland Clinic Conflict of Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the International Anesthesia Research Society. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1213/ANE.00000000000003482

Interest Policy. Edwards Lifesciences was not involved in protocol development, data management, or statistical analysis.

Conflicts of Interest: See Disclosures at the end of the article.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.anesthesia-analgia.org).

Trial Registration: ClinicalTrials.gov (NCT02872896).

Reprints will not be available from the authors.

Address correspondence to Kamal Maheshwari, MD, MPH, Department of General Anesthesiology, Outcomes Research, Anesthesiology Institute, Cleveland, Clinic, 9500 Euclid Ave, E-31, Cleveland, OH 44195. Address e-mail to maheshk@ccf.org.

Intraoperative blood pressure is usually measured intermittently using noninvasive oscillometric devices every 3–5 minutes. Continuous monitoring facilitates early diagnoses of hypotension, thus potentially promoting timely treatment. However, invasive blood pressure monitoring, which provides continuous blood pressure, is used in selected high-risk patients. An alternative is noninvasive finger cuff monitoring which can provide continuous hemodynamic monitoring. The ClearSight (Edwards Lifesciences Corp, Irvine, CA) is a continuous noninvasive hemodynamic monitor which uses volume clamp and physical methods.^{11–13} Absolute pressures obtained from this monitor are comparable to invasive blood pressure monitoring,^{12,14} and noninferior to oscillometric¹¹ methods. The system provides continuous beat-to-beat blood pressure, along with stroke volume, stroke volume variation, cardiac output, and systemic vascular resistance.¹⁵

We hypothesized that continuous noninvasive monitoring of blood pressure in moderate-to-high-risk surgical patients reduces the duration and severity of intraoperative hypotension compared to intermittent noninvasive blood pressure monitoring. Specifically, we tested the primary hypothesis that continuous hemodynamic monitoring reduces time-weighted average intraoperative MAP (TWA MAP) under a threshold of 65 mm Hg, a measure that characterizes both the duration and severity of hypotension (“amount of hypotension”). Secondarily, we tested the hypotheses that use of continuous hemodynamic monitoring resulted in lower TWA MAP <60 and <55 mm Hg.

METHODS

This study was approved by the Cleveland Clinic Institutional Review Board (IRB #16–845) and written informed consent was obtained from all subjects participating in the trial. The trial was registered before patient enrollment at clinicaltrials.gov (NCT02872896), principal investigator: Kamal Maheshwari, date of registration: August 19, 2016. We enrolled 320 adults, 45 years or older, with American Society of Anesthesiologists physical status III or IV who had moderate-to-high-risk noncardiac surgery with general anesthesia between August 2016 and August 2017. Patients were excluded if the attending anesthesiologist determined that invasive arterial monitoring was needed. Additionally, patients were excluded when there was >10% discrepancy in preoperative MAP between arms or the expected duration of surgery was <2 hours.

Shortly before induction of anesthesia, patients were randomly allocated to continuous unblinded or blinded continuous monitoring by an investigator not involved in clinical care, in a 1:1 ratio, using a reproducible set of computer-generated random number via a web-based system (REDCap secure web application). The allocation was thus concealed until the last minute, and patients were not informed of their group assignments.

The continuous monitor was placed on all patients in addition to the intermittent oscillometric cuff on opposite arms. In the continuous monitoring group, information from the continuous monitor was available to the clinicians in addition to the usual oscillometric values. In the blinded group, blood pressure management was based only on intermittent oscillometric blood pressure monitoring; the information from continuous monitors was not available to the

clinicians but recorded for analysis purposes. Oscillometric measurements were typically obtained at 5-minute intervals; clinicians were free to select any interval and to change it as conditions warranted.

All patients were monitored according to standards (electrocardiography, noninvasive blood pressure, oxygen saturation, temperature). Standard anesthetic management include etomidate (0.2–0.3 mg/kg) or propofol (1–2 mg/kg), vecuronium (0.1 mg/kg) or rocuronium (0.6 mg/kg), and fentanyl (1–2 µg/kg) at induction. Anesthesia subsequently was maintained with inhalational anesthetics (up to 1.5 minimum alveolar concentration) in a carrier gas of 50%–80% inspired oxygen and air. Clinicians were asked to minimize the amount and severity of hypotension <65 mm Hg MAP. However, the study protocol did not specify any particular approach. Clinicians were thus free to use any type and amount of intravenous fluids, whatever dose of vasopressors and inotropes they cared to, and to adjust the inhalational concentration and intravenous anesthetic drugs as necessary. Generally, we use intermittent bolus of phenylephrine and ephedrine to support blood pressure.

The continuously measured monitor MAP was used for analysis in both study groups. Blood pressures were assumed to be artifact and were removed using the following sequential rules: (1) blood pressures were documented by clinicians as artifact; (2) the systolic pressure was >300 mm Hg or <20 mm Hg; (3) the systolic pressure was less than diastolic pressure plus 5 mm Hg; or (4) the diastolic pressure was <5 mm Hg or >225 mm Hg. After removing artifacts, the TWA MAP under a threshold of 65 mm Hg was calculated as the area between 65 mm Hg threshold and the curve of the MAP measurements divided by total continuous reading time:

TWA MAP < 65 mm Hg =

$$\frac{\sum_{i=1}^k (\text{area}_1 < 65) + (\text{area}_2 < 65) + \dots + (\text{area}_k < 65)}{\text{total time of measurements}} \text{ mm Hg}$$

TWA is similar to an ordinary arithmetic mean, except that instead of each of the MAP measures contributing equally to the final average, some MAP measures contributed more than others. Two MAP measures with a longer time interval in-between those (due to removed MAP artifacts or missing MAP measurements) contributed more into the TWA than 2 MAP measures with shorter time interval in-between. Figure 1 shows an example of intraoperative MAP over time and calculation of the TWA MAP <65 mm Hg.

AKI was identified based on Acute Kidney Injury Network classification, modified per Walsh to exclude urine output.⁴ We also extended the normal 48-hour creatinine window used in the Acute Kidney Injury Network criteria to 7 days to better characterize the postoperative period.

Quality of recovery (QOR-15)¹⁶ and postoperative morbidity survey (POMS)¹⁷ were administered on the third postoperative day or at discharge based on which occurrence came first, by a blinded research fellow. QOR evaluates 5 dimensions: emotional state, physical discomfort, psychological support, physical independence, and pain.

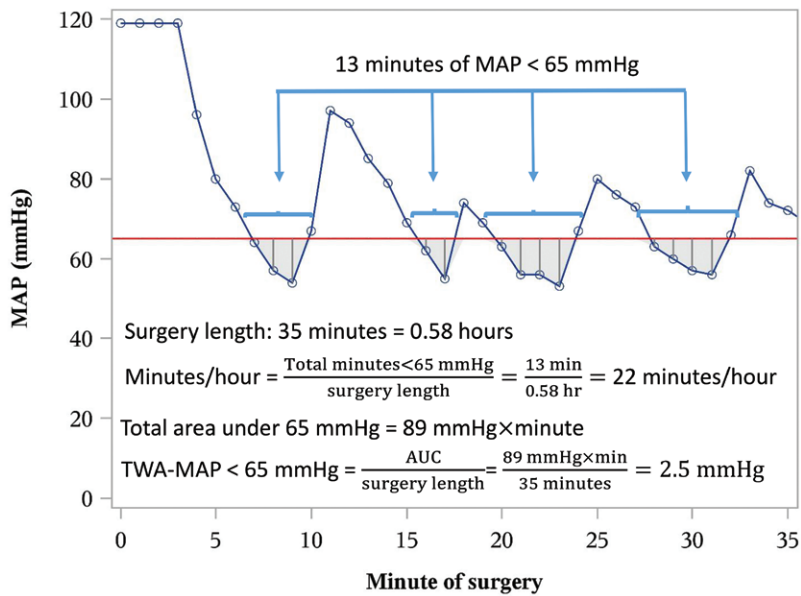


Figure 1. An example of intraoperative mean arterial pressure over surgical time and calculation of the time-weighted average mean arterial pressure (TWA MAP) <65 mm Hg. AUC indicates area under the curve.

The POMS, an 18-item survey that addresses 9 domains of postoperative morbidity, is a reliable and valid descriptor of short-term postoperative morbidity.

Statistical Analysis

First, we compared 2 randomized groups, continuous monitoring (unblinded) versus blinded, for balance on potentially confounding baseline and surgical characteristics using univariable summary statistics (mean and standard deviation, median and quartiles, or proportions, as appropriate) and using absolute standardized difference scores (ASDs). ASDs are defined as the absolute value of the difference among means, mean rankings, or proportions divided by a combined estimate of standard deviation; thus the ASD roughly represents the number of standard deviations the 2 study groups are apart from one another. We conservatively considered an ASD >0.20 as indicative of potential confounding and would adjust for such factors directly in the analyses comparing the groups on the outcome.

For primary analysis, 2 randomized groups were compared on the TWA MAP <65 mm Hg. We estimated the effect of continuous monitoring on TWA MAP drop using the 2-sample Wilcoxon rank-sum test and Hodges Lehmann estimation of location shift with corresponding asymptotic 95% CI. This method is appropriate because the TWA MAP drop <65 mm Hg exhibits a skewed distribution with many patients (25% of patients) having TWA MAP drop of zero. Additionally, the primary result was adjusted for slightly imbalanced age and type of surgery via multivariable generalized linear model with logit link function. To accommodate highly skewed zero-inflated outcome, we used gamma distribution; we substituted zeros with small nonzero value for the modeling purposes.

Analogously, we conducted 2 secondary analyses, in which the outcomes TWA MAP under MAP <60 mm Hg and MAP <55 mm Hg were evaluated. Six exploratory outcomes including transfusion requirement, AKI, in-hospital composite of death, stroke, or myocardial injury after non-cardiac surgery, QOR score, POMS, and hospital lengths

of stay were reported separately for 2 study groups using summary statistics without formal testing for statistical significance. The *P* value significance criteria for the primary final analysis was at *P* < .048 that included adjustment for the 1 interim analysis that was conducted. We used the Bonferroni adjustment for multiple outcomes to preserve the type I error at 5% level for the secondary analysis with the significance criterion of 0.024 for each of the secondary outcome (ie, 0.048/2). SAS statistical software version 9.4 (SAS Institute, Cary, NC) for 64-bit Microsoft Windows was used for data retrieval and statistical analysis.

Sample Size Consideration

Assuming a standard deviation of 0.8 mm Hg,⁹ the sample size of *N* = 133 patients per group (*N* = 266 patients total) would provide about 90% power at the 0.05 significance level to detect the difference of 0.32 or larger in TWA <65 mm Hg between 2 study groups. We also planned for 1 interim analyses at 50% of the planned enrollment; therefore, interim-adjusted sample size was *N* = 143 patients per group or *N* = 286 total. Group sequential design was used to test for efficacy and futility. We used the gamma spending function with parameters -4 and -1 for α (efficacy) and β (futility), respectively.

Assuming the drop-out rate of about 10% (due to surgery cancellation, a surgeon or anesthesiologist's last moment refusal, patient's withdrawal, and other unexpected events), we planned to enroll 158 patients in each group, a total of 316 patients. In addition, we planned for 4 pilot patients (2 per group) in the beginning of the study. Therefore, we anticipated enrolling 160 patients in each group for a total of *N* = 320 patients.

RESULTS

The analysis was intention-to-treat with postrandomization exclusion of cases. We included all randomized patients who were attached to a continuous monitor and had at least 1 record of continuous blood pressure between induction and emergence timestamps, that is, all patients who

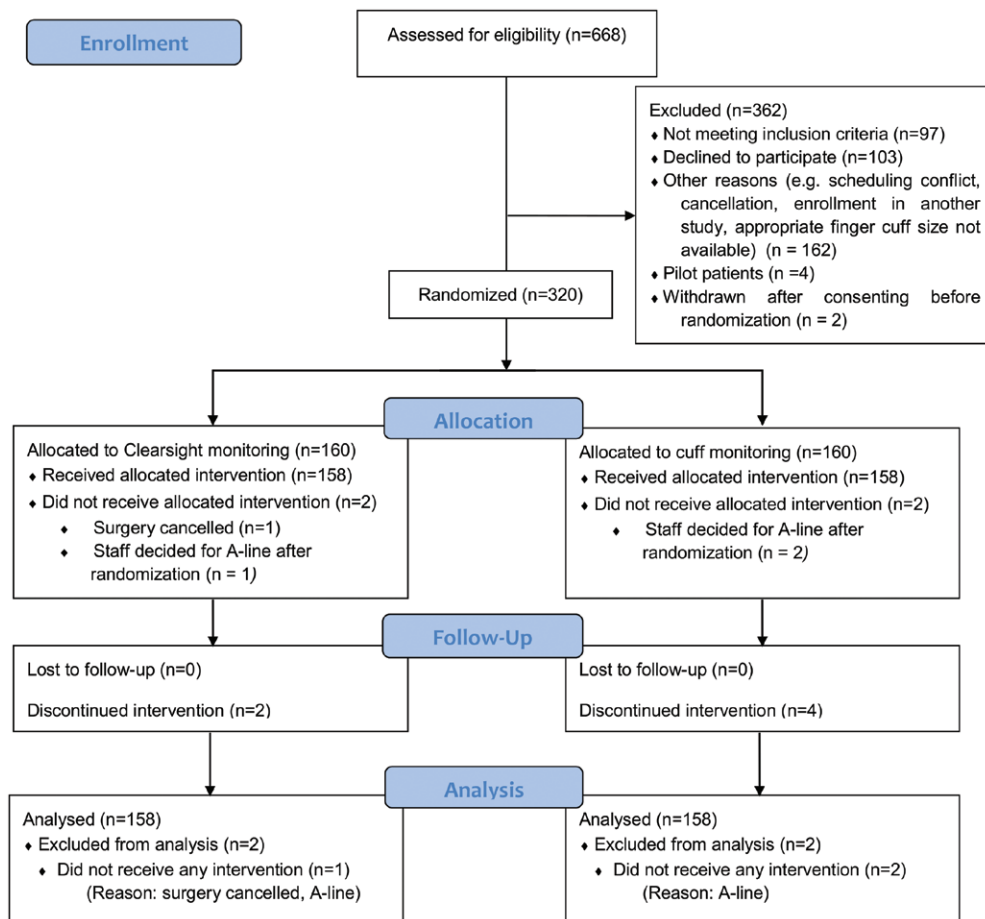


Figure 2. Randomized trial diagram.

received continuous monitoring and had a primary outcome recorded.

Among 320 randomized patients, 4 were not included in the analysis because they did not experience a study exposure: in 3 cases, the staff anesthesiologist decided to use invasive arterial monitoring after randomization (exclusion criteria) before the procedure started and did not attach the continuous monitor; 1 surgery was cancelled after randomization (Figure 2). Thus, per intention-to-treat, data from 316 patients were available for the final analysis with 158 (50%) randomized to continuous monitoring (unblinded) group, and 158 (50%) to intermittent oscillometric blood pressure monitoring (blinded) group. The summary of the demographic, baseline, and surgical characteristics is reported in Table 1. The randomized groups were balanced on all baseline variables; none of baseline variables were included as covariables in the analysis. Some intraoperative characteristics are summarized in Table 2.

The blood pressure primary and secondary outcomes along with additional blood pressure descriptions are reported in Table 3. The use of continuous monitoring resulted in significantly lower TWA MAP <65 mm Hg threshold in the continuous monitoring (unblinded) 0.05 [0.00, 0.22] mm Hg compared to 0.11 [0.00, 0.54] mm Hg blinded group ($P = .039$, significance criteria $P < .048$). The estimated location shift (the nonparametric version of difference in means) was 0.03 (95% CI, 0.00–0.06, continuous

monitoring [unblinded] versus blinded) mm Hg. After adjustment for slightly imbalanced age and type of surgery, the conclusion was consistent with univariate analysis ($P = .035$). The treatment effect on TWA MAP <60 mm Hg threshold was in the same direction, but was not statistically significant 0.01 [0.00, 0.08] mm Hg continuous monitoring (unblinded) versus 0.02 [0.00, 0.22] mm Hg blinded group ($P = .035$, significance criteria $P < .024$). Continuous monitoring use was associated with improved TWA MAP <55 mm Hg threshold in continuous monitoring (unblinded) group 0.00 [0.00,0.02] mm Hg versus blinded group 0.00 [0.00,0.07] mm Hg ($P = .017$, significance criteria $P < .024$). The intraoperative time patients spent below MAP thresholds in each study groups are summarized in Figure 3. The exploratory outcomes are reported in Supplemental Digital Content, Table 1, <http://links.lww.com/AA/C418>.

DISCUSSION

Continuous noninvasive blood pressure monitoring in moderate-to-high-risk surgical patients reduced the duration and severity of hypotension compared to intermittent blood pressure monitoring as indicated by significantly lower TWA MAP <65 mm Hg. Additionally, the median time spent <65 mm Hg was nearly halved (2 vs 4 minutes) in the continuous monitoring group, although we did not formally compare the 2 groups on duration of hypotension outcome. The amounts of hypotension were also lower

Table 1. The Demographic, Baseline, and Surgical Characteristics of the Study Population (N = 316)			
Factor	Continuous Monitoring (Unblinded) (N = 158)	Blinded (N = 158)	ASD
Demographic and baseline characteristics			
Age (y)	59.9 (8.6)	61.7 (9.0)	0.20
Female (%)	80/158 (51%)	77/158 (49%)	0.04
BMI (kg/m ²) ^a	33.4 (9.8)	33.6 (8.9)	0.02
Race (%) ^a			0.15
Caucasian	129/151 (85%)	141/158 (89%)	
African American	21/151 (14%)	15/158 (10%)	
Other	1/151 (1%)	2/158 (1%)	
ASA physical status			0.17
I-II	24/158 (15%)	16/158 (10%)	
III	131/158 (83%)	137/158 (87%)	
IV	3/158 (2%)	5/158 (3%)	
Baseline creatinine ^a	0.95 [0.79, 1.1]	0.90 [0.79, 1.06]	0.08
Baseline MAP (mm Hg) left arm ^a	95 [87, 103]	97 [88, 105]	0.13
Baseline MAP (mm Hg) right arm ^a	95 [87, 104]	96 [89, 104]	0.15
Site of ClearSight cuff placement			0.15
Left	80/158 (50.6%)	75/158 (47.5%)	
Right	69/158 (43.7%)	78/158 (49.4%)	
Missing	9/158 (5.7%)	5/158 (3.2%)	
Heart rate before induction (bpm) ^a	76 [68, 84]	75 [67, 85]	0.01
MAP before induction (mm Hg) ^a	94 [90, 100]	95 [89, 101]	0.05
Medical history			
COPD (%) ^a	20/158 (12.7%)	20/157 (12.7%)	0.00
Aortic stenosis (%)	0/158 (0.0%)	0/158 (0.0%)	
Obesity (%) ^a	93/157 (59.2%)	84/158 (53.2%)	0.12
Diabetes mellitus (%) ^a	44/158 (27.8%)	39/157 (24.8%)	0.07
Dialysis (%)	0/158 (0.0%)	0/158 (0.0%)	
Surgery characteristics			
General anesthesia + block (versus general anesthesia only)	13/158 (8.2%)	12/158 (7.6%)	0.02
Induction propofol use	157/158 (99.4%)	156/158 (98.7%)	0.07
Propofol (mg)	200 [170, 300]	200 [180, 290]	0.09
Intraoperative opioids/anxiolytics			
Midazolam (mg)	2.0 [1.0, 2.0]	2.0 [0.0, 2.0]	0.16
Fentanyl (mg)	0.23 [0.18, 0.25]	0.20 [0.15, 0.25]	0.06
Hydromorphone (mg)	0.00 [0.00, 0.80]	0.00 [0.00, 0.40]	0.10
Remifentanyl (mg)	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.11
Meperidine (mg)	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00
Morphine equivalents (mg)	25.0 [20.0, 30.0]	24.6 [20.0, 30.0]	0.09
Surgery type (%)			0.22
Orthopedic	7/158 (4.4%)	11/158 (7.0%)	
Urology	60/158 (38.0%)	55/158 (34.8%)	
GYN	14/158 (8.9%)	19/158 (12.0%)	
Colorectal	22/158 (13.9%)	21/158 (13.3%)	
General	26/158 (16.5%)	18/158 (11.4%)	
Bariatrics	29/158 (18.4%)	34/158 (21.5%)	
Surgery duration	219 [176, 276]	224 [169, 278]	0.02

Statistics presented as mean (standard deviation), median [first quartile, third quartile], or N/total number of patients (%), as appropriate.

Abbreviations: ASA, American Society of Anesthesiologists; ASD; absolute standardized difference score; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GYN, gynecology; MAP mean arterial pressure.

^aData are not available for all subjects. Missing values: BMI = 1, race = 7, COPD = 1, obesity = 1, diabetes mellitus = 1, heart rate before induction (bpm) = 6, MAP before induction (mm Hg) = 6, baseline creatinine = 33, baseline MAP (mm Hg) left arm = 17, baseline MAP (mm Hg) right arm = 17.

under thresholds of 60 and 55 mm Hg in the continuous monitoring group.

Our results suggest that early detection of hypotension prompts remedial steps, thus reducing the overall duration and severity of intraoperative hypotension. The differences in TWA MAP are relatively small but even few minutes of extra hypotension is associated with worse outcome.^{9,10} For example, just a single minute at a MAP of 50 mm Hg increases the risk of mortality 5%.¹⁰

Our results are consistent with Meidert et al,¹⁸ who randomized 160 orthopedic surgery patients to continuous blood pressure monitoring or monitoring every 3 minutes

and reported that continuous monitoring improved hemodynamic stability. However, Meidert et al¹⁸ used the oscillometric blood pressure values every 3 minutes for the first hour of general anesthesia; in contrast, we compared continuous blood pressure measurements every 20 seconds throughout surgery. Benes et al¹⁹ also reported that continuous monitoring reduced time below -20% of baseline pressure in 40 randomized thyroid surgical patients: 12 (4-20) vs 27 minutes (16-34); $P = .001$.

We chose TWA MAP to measure hypotension because it best represents both the duration and severity of hypotension. Furthermore, 65 mm Hg appears to be a critical

Table 2. Intraoperative and Postoperative Patient Characteristics of the Study Population (N = 316)

Intraoperative Characteristics	Continuous Monitoring (Unblinded) (N = 158)	Blinded (N = 158)
Volatile anesthetic dose (MAC-h) ^a	2.8 [2.2, 3.6]	2.9 [2.2, 3.7]
Intraoperative fluid volume administered		
Colloids (mL)	0 [0, 500]	0 [0, 250]
Crystalloids (mL)	2200 [1700, 2900]	2200 [1800, 2700]
Red blood cell transfusion (%)	2/158 (1.3%)	4/158 (2.5%)
Platelet transfusion (%)	0/158 (0%)	0/158 (0%)
Vasopressor drug		
Ephedrine use (%)	76/158 (48%)	69/158 (44%)
Ephedrine dose (mg) ^b	10 [8.6; 20]	15 [10; 20]
Phenylephrine use (%)	103/158 (65%)	93/158 (59%)
Phenylephrine dose (mg) ^b	0.35 [0.20; 0.70]	0.40 [0.20; 0.95]
Estimated blood loss (mL)	100 [30, 250]	100 [50.0, 200]
Urine output (mL)	168 [50, 380]	200 [50.0, 350]
Hemodynamic and respiratory parameters		
Heart rate (bpm)	72/158 (9%)	73/158 (10%)
SpO ₂ (%)	97/158 (2%)	97/158 (2%)
Discharge disposition (%)		
PACU	157/158 (99.4%)	155/158 (98.1%)
ICU	1/158 (0.6%)	1/158 (0.6%)
Other ^c	0 (0%)	2/158 (1.3%)

Statistics presented as mean (standard deviation), median [first quartile, third quartile], or N/total number of patients (%), as appropriate.

Abbreviations: ICU; intensive care unit; MAC, minimum alveolar concentration; PACU, postoperative care unit; SpO₂, oxygen saturation.

^aVolatile anesthetic dose is missing in 6 patients.

^bDose was calculated only for patients who received the intraoperative medication.

^cPatient was discharged to the PACU for 2 h, followed by transfer to the surgical intensive care unit.

Table 3. Summary of Blood Pressure Outcomes (N = 316)

Outcomes	Continuous Monitoring (Unblinded) (N = 158)	Continuous Monitoring (Blinded) (N = 158)	Location Shift ^a (95% CI) ^b	P Value ^c
Noninvasive reading (min)	196 (79)	190 (84)		
Number of ClearSight BP readings	588 (236)	571 (252)		
Primary outcome				
TWA MAP <65 mm Hg (mm Hg)	0.05 [0.00, 0.22]	0.11 [0.00, 0.54]	0.03 (0.00, 0.06)	.039 ^c
Number of patients with any MAP readings <65 mm Hg	119/158 (75%)	120/158 (76%)		
Duration of MAP <65 mm Hg (min)	2.3 [0.3, 7.7]	4.0 [0.3, 14]		
AUC MAP <65 mm Hg	9.5 [0.33, 39.7]	20.0 [0.67, 75.3]		
Secondary outcomes				
TWA MAP <60 mm Hg (mm Hg)	0.01 [0.00, 0.08]	0.02 [0.00, 0.22]	0.005 (0.00, 0.01)	.035
Number of patients with any MAP readings <60 mm Hg	91/158 (58%)	99/158 (63%)		
Duration of MAP <60 mm Hg (min)	0.3 [0, 2.7]	1.3 [0, 5.3]		
AUC MAP <60 mm Hg	1.5 [0.00, 13.0]	3.3 [0.00, 34.3]		
TWA MAP <55 mm Hg (mm Hg)	0.00 [0.00, 0.02]	0.00 [0.00, 0.07]	0.00 (0.00, 0.00)	.017 ^c
Number of patients with any MAP readings <55 mm Hg	58/158 (37%)	76/158 (48%)		
Duration of MAP <55 mm Hg (min)	0 [0, 0.7]	0 [0, 2.7]		
AUC MAP <55 mm Hg	0.00 [0.00, 2.7]	0.00 [0.00, 12.3]		

Statistics presented as mean (standard deviation), median [first quartile, third quartile], or N/total number of patients (%), as appropriate.

For the primary analysis, we compared continuous monitoring (unblinded) and blinded randomized groups on TWA MAP drop <65 mm Hg outcome using Wilcoxon rank-sum test; Hodges Lehmann estimation of location shift and 95% CI were reported.

Abbreviations: AUC, area under the curve; BP, blood pressure; CI, confidence interval; MAP, mean arterial pressure; TWA, time-weighted average.

^aLocation shift describes a difference in skewed TWA MAP <65 mm Hg outcome between 2 study groups; Hodges Lehmann estimation of location shift and asymptotic CI were reported.

^bConfidence limits reflect the correction for interim analyses to maintain overall type I error rate at 5%.

^cP value corresponded to Wilcoxon rank-sum test. For the primary outcome, P value significance criteria was at P < .048 that included adjustment for the performed earlier interim analysis. For the secondary outcomes, P value significance criteria was at P < .024 that included adjustment for the interim analysis and 2 secondary outcomes.

threshold below which risk increases substantially.^{4,9,10} The TWA <65 of 0.11 mm Hg in the oscillometric group means that the average patient had an exposure 0.11 mm Hg below 65 mm Hg throughout surgery. With an average case duration in the study of nearly 4 hours, a TWA MAP of 0.11 corresponds to 0.11 mm Hg times 240 minutes = 26 mm Hg × minutes. In this example, 26 mm Hg-minutes could refer to

a patient who spent 13 minutes at 63 mm Hg or approximately 4 minutes at 59 mm Hg.

The ultimate goal of any intraoperative intervention is to improve postoperative outcomes. Because this study was not designed to assess postoperative outcomes, we report major complications without statistical analysis. Possibly this information will help guide much larger future randomized trials.

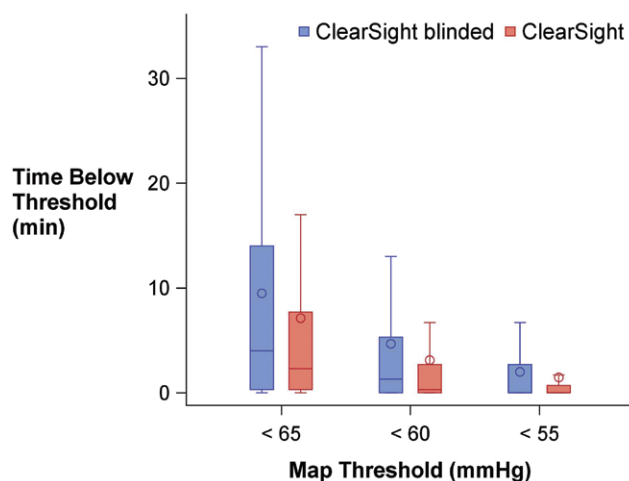


Figure 3. Intraoperative time patients spent below mean arterial pressure (MAP) thresholds of 65, 60, and 55 mm Hg.

Once hypotension is detected, the optimal treatment is often unclear and depends on numerous factors. Advanced hemodynamic parameters can guide management of hypotension and help clinicians determine whether to augment vascular volume, reduce anesthetic administration, or use vasopressors or inotropes. The noninvasive continuous blood pressure monitor we used also estimates various advanced hemodynamic variables including stroke volume, stroke volume variation, cardiac output, and systemic vascular resistance. Because there is no particular protocol for managing blood pressure, we do not know to what extent clinicians considered these ancillary measures.

The impact of continuous monitoring may have been limited by lack of set protocol for hypotension management. Clinicians may also have mistrusted the accuracy of ClearSight blood pressure and ancillary measurements, despite good validation.

Interestingly, there was less overall hypotension even in our blinded cohort than in previous reports from our own institution. For example, in a large observational study¹⁰ that included 152,445 adult noncardiac surgery patients, the time <65 mm Hg was 10 [2, 25] minutes compared to 4 [0.3, 14] minutes. There are at least 3 potential explanations. First, the current study population was restricted to American Society of Anesthesiologists physical status III–IV patients who had major surgery and did not require continuous pressure monitoring. While that excludes lower-risk patients, it also excluded high-risk patients who would normally have invasive pressure monitoring. Second, clinicians were specifically instructed to limit MAP <65 mm Hg. And third, clinicians in our department are well aware of recent publications showing strong associations between hypotension and myocardial and renal injury. It is likely that they are now tolerating less hypotension than previously.

In summary, continuous noninvasive blood pressure monitoring nearly halved the amount of intraoperative hypotension in adults having noncardiac surgery, presumably because continuous monitoring allowed clinicians to detect hypotension earlier and respond effectively. Given that even few minutes of hypotension is associated with myocardial and kidney injury, avoiding hypotension

may well reduce the incidence of serious complications—although this theory remains to be confirmed in much larger trials. ■■

DISCLOSURES

Name: Kamal Maheshwari, MD, MPH.

Contribution: This author helped devise the concept and design of the study. He analyzed and interpreted the data, wrote the first draft, revised the manuscript and gave the final approval of the version to be published, and was the principal investigator of this trial.

Conflicts of Interest: K. Maheshwari is a consultant for Edwards Lifescience.

Name: Sandeep Khanna, MD.

Contribution: This author helped conduct and coordinate the trial. He devised the concept and design of the study, wrote the first draft, revised the manuscript and gave the final approval of the version to be published, and was a coinvestigator of this trial.

Conflicts of Interest: None.

Name: Gausan Ratna Bajracharya, MD.

Contribution: This author helped conduct and coordinate the trial. He collected the data, revised the manuscript and gave the final approval of the version to be published, and was the lead coordinator of this trial.

Conflicts of Interest: None.

Name: Natalya Makarova, MS.

Contribution: This author helped write the statistical analysis plan, collected data and did the statistical analyses, revised it critically for important intellectual content, gave the final approval of the version to be published, and was the biostatistician of this trial.

Conflicts of Interest: None.

Name: Quinton Riter, BS.

Contribution: This author helped conduct the trial, collect the data, revise the manuscript critically for important intellectual content, and gave the final approval of the version to be published.

Conflicts of Interest: None.

Name: Syed Raza, BS.

Contribution: This author helped conduct the trial, collect the data, revise the manuscript critically for important intellectual content, and gave the final approval of the version to be published.

Conflicts of Interest: None.

Name: Jacek B. Cywinski, MD.

Contribution: This author helped conduct and coordinate the trial. He devised the concept and design of the study, revised the manuscript, gave the final approval of the version to be published, and was a coinvestigator of this trial.

Conflicts of Interest: None.

Name: Maged Argalious, MD, MBA, MEd, FASE.

Contribution: This author helped conduct and coordinate the trial. He devised the concept and design of the study, revised the manuscript, gave the final approval of the version to be published, and was a coinvestigator of this trial.

Conflicts of Interest: None.

Name: Andrea Kurz, MD.

Contribution: This author helped conduct and coordinate the trial. She devised the concept and design of the study, revised the manuscript, gave the final approval of the version to be published, and was a coinvestigator of this trial.

Conflicts of Interest: A. Kurz is a consultant for Edwards Lifescience.

Name: Daniel I. Sessler, MD.

Contribution: This author helped analyze and interpret the data, revised it critically for important intellectual content, and gave the final approval of the version to be published.

Conflicts of Interest: D. I. Sessler is a consultant for Edwards Lifescience.

This manuscript was handled by: Richard C. Prielipp, MD.

REFERENCES

1. Devereaux PJ, Yang H, Yusuf S, et al; POISE Study Group. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet*. 2008;371:1839–1847.

2. Lienhart A, Auroy Y, Péquignot F, et al. Survey of anesthesia-related mortality in France. *Anesthesiology*. 2006;105:1087–1097.
3. Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. *Anesth Analg*. 2005;100:4–10.
4. Walsh M, Devereaux PJ, Garg AX, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology*. 2013;119:507–515.
5. Monk TG, Bronsert MR, Henderson WG, et al. Association between intraoperative hypotension and hypertension and 30-day postoperative mortality in noncardiac surgery. *Anesthesiology*. 2015;123:307–319.
6. Sun LY, Wijeyesundera DN, Tait GA, Beattie WS. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. *Anesthesiology*. 2015;123:515–523.
7. Futier E, Lefrant JY, Guinot PG, et al; INPRESS Study Group. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. *JAMA*. 2017;318:1346–1357.
8. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ. Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. *Anesthesiology*. 2007;107:213–220.
9. Salmasi V, Maheshwari K, Yang D, et al. Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery: a retrospective cohort analysis. *Anesthesiology*. 2017;126:47–65.
10. Stapelfeldt WH, Yuan H, Dryden JK, et al. The SLUScore: a novel method for detecting hazardous hypotension in adult patients undergoing noncardiac surgical procedures. *Anesth Analg*. 2017;124:1135–1152.
11. Eeftinck Schattenkerk DW, van Lieshout JJ, van den Meiracker AH, et al. Nexfin noninvasive continuous blood pressure validated against Riva-Rocci/Korotkoff. *Am J Hypertens*. 2009;22:378–383.
12. Martina JR, Westerhof BE, van Goudoever J, et al. Noninvasive continuous arterial blood pressure monitoring with Nexfin®. *Anesthesiology*. 2012;116:1092–1103.
13. Wesseling K, De Wit B, Van der Hoeven G, van Goudoever J, Settles J. Physiocal, calibrating finger vascular physiology for Finapres. *Homeostasis*. 1995;36:67–82.
14. Westerhof BE, Guelen I, Parati G, et al. Variable day/night bias in 24-h non-invasive finger pressure against intrabrachial artery pressure is removed by waveform filtering and level correction. *J Hypertens*. 2002;20:1981–1986.
15. Bogert LW, Wesseling KH, Schraa O, et al. Pulse contour cardiac output derived from non-invasive arterial pressure in cardiovascular disease. *Anaesthesia*. 2010;65:1119–1125.
16. Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology*. 2013;118:1332–1340.
17. Grocott MP, Browne JP, Van der Meulen J, et al. The postoperative morbidity survey was validated and used to describe morbidity after major surgery. *J Clin Epidemiol*. 2007;60:919–928.
18. Meidert AS, Nold JS, Hornung R, Paulus AC, Zwißler B, Czerner S. The impact of continuous non-invasive arterial blood pressure monitoring on blood pressure stability during general anaesthesia in orthopaedic patients: a randomised trial. *Eur J Anaesthesiol*. 2017;34:716–722.
19. Benes J, Simanova A, Tovarnicka T, et al. Continuous non-invasive monitoring improves blood pressure stability in upright position: randomized controlled trial. *J Clin Monit Comput*. 2015;29:11–17.