ANESTHESIOLOGY

Hypotension Prediction Index for Prevention of Hypotension during Moderate- to High-risk Noncardiac Surgery

A Pilot Randomized Trial

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ABSTRACT

Background: The Hypotension Prediction Index is a commercially available algorithm, based on arterial waveform features, that predicts hypotension defined as mean arterial pressure less than 65 mmHg for at least 1 min. We therefore tested the primary hypothesis that index guidance reduces the duration and severity of hypotension during noncardiac surgery.

Methods: We enrolled adults having moderate- or high-risk noncardiac surgery with invasive arterial pressure monitoring. Participating patients were randomized to hemodynamic management with or without index guidance. Clinicians caring for patients assigned to guidance were alerted when the index exceeded 85 (range, 0 to 100) and a treatment algorithm based on advanced hemodynamic parameters suggested vasopressor administration, fluid administration, inotrope administration, or observation. Primary outcome was the amount of hypotension, defined as time-weighted average mean arterial pressure less than 65 mmHg. Secondary outcomes were time-weighted mean pressures less than 60 and 55 mmHg.

Results: Among 214 enrolled patients, guidance was provided for 105 (49%) patients randomly assigned to the index guidance group. The median (first quartile, third quartile) time-weighted average mean arterial pressure less than 65 mmHg was 0.14 (0.03, 0.37) in guided patients *versus* 0.14 (0.03, 0.39) mmHg in unguided patients: median difference (95% CI) of 0 (–0.03 to 0.04), $P = 0.757$. Index guidance therefore did not reduce amount of hypotension less than 65 mmHg, nor did it reduce hypotension less than 60 or 55 mmHg. *Post hoc*, guidance was associated with less hypotension when analysis was restricted to episodes during which clinicians intervened.

Conclusions: In this pilot trial, index guidance did not reduce the amount of intraoperative hypotension. Half of the alerts were not followed by treatment, presumably due to short warning time, complex treatment algorithm, or clinicians ignoring the alert. In the future we plan to use a lower index alert threshold and a simpler treatment algorithm that emphasizes prompt treatment.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Hypotension prediction algorithms commonly use arterial waveform features derived from arterial blood pressure monitoring. Whether they reduce the duration and severity of hypotension, especially in noncardiac surgery, is unknown.

What This Article Tells Us That Is New

- Of 214 noncardiac surgical patients, 105 (49%) patients randomized to management with a hypotension prediction algorithm, intraoperative hypotension was not reduced compared with controls. A lower alert threshold enabling adequate warning time and a simpler treatment algorithm that emphasizes prompt treatment after alert may help.

Intraoperative hypotension is common during noncardiac surgery.[1] Most patients experience at least one episode during which mean arterial pressure (MAP) decreases to less than 65 mmHg, often shortly after anesthetic induction.[2,3] Intraoperative hypotension is associated with worse postoperative outcomes including myocardial infarction, acute kidney injury, and mortality.[4–7] In a recent randomized controlled trial, Futier *et al.* reported that preventing intraoperative hypotension reduces the risk of postoperative organ dysfunction by about 25%,[8] suggesting that the association between hypotension and organ injury is at least partially causal and therefore potentially amenable to intervention.

Presumably, reducing the frequency, depth, and duration of intraoperative hypotension would reduce organ injury. During surgery, anesthesia clinicians respond to blood pressure trends and treat hypotension as necessary, mostly when it occurs. It is difficult to predict hypotension; therefore,

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despite a clinician's best efforts, preventing all intraoperative hypotension is difficult.

The Hypotension Prediction Index algorithm on the EV1000 system (Edwards Lifesciences, USA) uses arterial waveform features including waveform time, amplitude, area, segment slopes, and complexity features to predict hypotension, defined by MAP less than 65 mmHg for at least 1 min.[9] The index values ranges from 0 to 100, with higher numbers reflecting a higher likelihood of subsequent hypotension. The system also provides advanced hemodynamic information including cardiac output, dynamic arterial elastance, dP/dtmax (systolic slope), and stroke volume—which presumably helps clinicians select optimal treatments. The index reportedly has 92% sensitivity and specificity for predicting hypotension 5 min in advance; sensitivity was 89% and specificity 90% for 10 min in advance, and was 88% and 87% for 15 min in advance.[9] The algorithm is cleared for sale in Europe and the United States.

Our randomized trial was *a priori* defined as a pilot to estimate treatment effect and between-patient variability. The primary hypothesis of our superiority trial was that index guidance compared to routine care reduces time-weighted average intraoperative hypotension below a MAP threshold of 65 mmHg in patients having moderate- to high-risk noncardiac surgery. Secondarily, we tested the hypotheses that index guidance reduces time-weighted average mean arterial pressure less than 60 and 55 mmHg.

Materials and Methods

Our trial was conducted at two Cleveland Clinic hospitals (Cleveland, Ohio) in accordance with Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and relevant regulatory requirements. The trial was registered in ClinicalTrials.gov, identifier, NCT03610165; Principal Investigator, Kamal Maheshwari; August 1, 2018. The Cleveland Clinic Institutional Review Board approved the trial, and we obtained written individual informed consent from each participant. The Department of Outcomes Research supported development of the protocol, managed conduct of the trial, collected and managed the data, monitored trial staff, and conducted the statistical analysis. The full protocol has been published[10] and is also available at maheshk@ccf.org on a collaborative basis.

We included adults 45 yr old or greater who were designated American Society of Anesthesiologists (ASA) physical status III or IV and had moderate- or high-risk noncardiac surgery as defined by the responsible anesthesiologist and planned invasive blood pressure monitoring. All had general anesthesia expected to last more than 2 h and planned overnight hospitalization. We excluded urgent/emergency procedures, patients with known clinically important intracardiac shunts, moderate to severe valvular disease, need of tidal volume less than 8 ml/kg of ideal body weight during surgery, current persistent atrial fibrillation, congestive heart failure with ejection fraction less than 35%, and neurosurgical procedures.

A research team member evaluated eligibility, obtained informed consent, and enrolled the participants. Shortly before surgery, patients were randomly assigned, stratified by study site, in a 1:1 ratio to index-guided (unblinded) or to unguided (blinded) groups. Randomization codes were generated using the PLAN procedure in using SAS/STAT software (SAS Institute Inc., USA) and implemented *via* a web-based system (REDCap secure web application; Vanderbilt University, Nashville, Tennessee). Allocation was thus concealed from patients, and patients were not informed of their group assignment.

The algorithm requires a "clean" arterial waveform. A research team member ensured the waveform was acceptable using fast flush test[11] at the beginning of each case. The test includes activation of a flush device creating sudden high pressure in the arterial pressure system followed by a sinusoidal wave to help identify appropriate dynamic response.

The index, which ranges from 0 to 100, is displayed on the EV1000 screen. All audible alarms were silenced in both groups. A research team member continuously monitored a hemodynamic monitor screen throughout the case. When the index reached 85 or above, the score flashed red, alerting an investigator who then reviewed advanced hemodynamic variables as per the treatment algorithm (Supplemental Digital Content 1, http://links.lww.com/ALN/C477) and recommended one of six treatment options to the clinicians; fluid plus vasopressor, fluid plus inotrope, fluid, vasopressor, inotrope and observe. Per protocol, clinicians were free to accept or reject the treatment.

The primary outcome was time-weighted average MAP less than 65 mmHg. We also characterized hypotension severity as area under the curve (AUC)–MAP less than 65 mmHg and minutes of MAP less than 65 mmHg. Secondary outcomes included the same measures, but under thresholds of 55 and 60 mmHg.

AUC-MAP below each threshold was calculated as the cumulative sum of the areas below the given threshold for a patient using the trapezoid rule and measured in units of mmHg times minutes. MAP measurements were recorded every 20 s by the EV1000 system. Calculation of a specific area started when MAP was less than 65 mmHg and ended when MAP was greater than 65 mmHg. Time-weighted average MAP below each threshold for each patient was derived by dividing AUC-MAP by the time interval between the first and the last MAP measurements. Time-weighted average MAP thus represents AUC-MAP normalized for the duration of anesthesia, in units of mmHg, or the average (over time) mmHg below the threshold.

Intraoperative exploratory outcomes included amount of erythrocyte transfusion, amount of intraoperative crystalloid and colloid, frequency of administration and dose of vasoactive medications (vasopressor; phenylephrine and norepinephrine, inotropes; epinephrine and ephedrine), blood loss, and urine output. Advanced hemodynamic variables including cardiac output, cardiac index, stroke volume,

and stroke volume variation were recorded every 20 s and downloaded directly from the EV1000 monitor.

Postoperative exploratory outcomes included postoperative acute kidney injury, Quality of Recovery-15[12] on postoperative day 3, Postoperative Morbidity Survey[13] on postoperative day 3, hospital length of stay after surgery, hospital readmission within 30 days, and a collapsed composite outcome (any *vs*. none) defined as the occurrence of any of three complications before hospital discharge including in-hospital death, in-hospital stroke, and myocardial injury after noncardiac surgery. Myocardial injury after noncardiac surgery was defined by maximum troponin (fourth-generation troponin T) greater than or equal to 0.03 ng/ml during the initial three postoperative days while hospitalized.

Statistical Analysis

Randomized groups were compared on baseline variables with standardized differences, which are differences in means or proportions divided by the pooled SD. Variables with absolute standardized difference more than $1.96 \times \sqrt{\frac{1}{n_1} + \frac{1}{n_2}} = 0.267$ were considered imbalanced, where $n_1 = 105$ and $n_2 = 108$ are the per group sample size.[14] We planned to adjust for any imbalanced baseline variables in all analyses.

The treatment effect of the index-guided *versus* unguided groups on the primary outcome of intraoperative time-weighted average MAP under a threshold of 65 mmHg was assessed using the Wilcoxon rank sum test, as the variable was not normally distributed. Randomized groups were compared on continuous secondary and exploratory continuous outcomes with either two-sample *t* test or Wilcoxon rank sum test, as appropriate. Groups were compared on binary outcomes with a chi-square test. Hospital length of stay was analyzed as a time-to-event variable (time to discharge alive; censoring deaths at the longest length of stay of any patient) using Kaplan–Meier analysis and comparing groups with the log-rank test.

Post Hoc *Analyses*. We measured the *time to hypotensive event* defined as the duration between the index exceeding 85 and subsequent hypotension (detailed algorithm in fig. 1). If no hypotension occurred within 15 min (which might be consequent to poor prediction, clinical interventions, or surgical manipulations), time to hypotension was considered undeterminable, and the episode (not the patient) was excluded from the duration analysis.

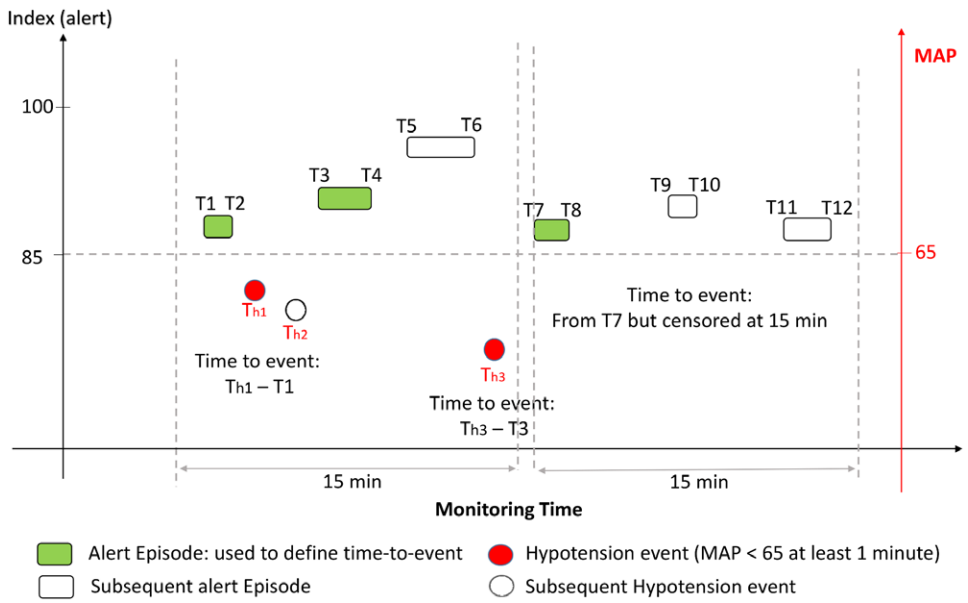

Fig. 1. Prediction alert and hypotension episode. Alert episode: defined as index value greater than 85 and previous index value less than or equal to 85 and all index values greater than 85, within the episode. Hypotensive event: consecutive MAP less than 65 for at least 1 min after the alert. Alert-to-hypotension episode: time to hypotensive event was the time from the first index value greater than 85 to the first MAP reading of the hypotensive event (if there are multiple subsequent hypotensive events within 15 min, the first hypotensive event is used; if there are multiple subsequent alert episodes before the first hypotensive event, the subsequent alert episode is ignored. If no hypotensive event occurred within 15 min (which can be caused by clinical interventions, or surgical manipulations stopping the development of hypotension), time to event for the episode is considered as undeterminable and therefore not included in the summary. In this example, only include three alert episodes (T1 to T2, T3 to T4, T7 to T8), and only two alert-to-hypotension episodes (Th1 to T1 and Th3 to T3). MAP, mean arterial pressure; T, time of alert, index greater than or equal to 85; Th, time of hypotension, MAP less than 65.

In the index-guided group, we also recalculated the time-weighted average, AUC, and duration of MAP under different thresholds (MAP less than 55, less than 60, and less than 65 mmHg) after excluding segments with no clinical intervention after index exceeding 85. Specifically, we removed MAP data from a patient's intraoperative MAP-over-time profile corresponding to "observe" segments, that is, periods in which the actual intervention selected by the responsible clinician was "observe" rather than any treatment. Observe periods extended from the time index exceeding 85 to the subsequent intervention or 10 min, whichever came first. Hypotension that occurred during an "observe" segment was thus not considered.

Finally, we used kappa coefficients to assess agreement beyond chance between interventions suggested by the treatment algorithm[10] and actual clinical interventions. Results were reported as observed agreement, expected agreement, and kappa. Potential interventions were (1) "fluid + vasopressor," (2) "fluid + inotrope," (3) "fluid," (4) "vasopressor," (5) "inotrope," and (6) "observe" (Supplemental Digital Content 1, http://links.lww.com/ALN/C477).

Sample Size Considerations

Using our institutional database, in a representative sample of patients having noncardiac surgery, we observed a mean (SD) AUC-MAP less than 65 of 80 (127) mmHg · min and median (quartiles) of 24 (1, 121) mmHg · min. The data were highly skewed, with a nontrivial proportion of zero values. We therefore used the nonparametric Wilcoxon rank sum test to estimate sample size.

A sample size of 213 would provide 80% power for detecting an approximate 20% relative reduction in the mean of the AUC-MAP less than 65 mmHg . min. Sample size for the primary outcome of time-weighted average MAP less than 65 mmHg was the same because time-weighted average MAP is simply the AUC-MAP divided by surgical duration, and in a randomized trial, the average surgical duration would be expected to be similar between groups as they were in the current study. Based on clinical judgment, we *a priori* decided that a 20% reduction would be clinically meaningful. All statistical tests were two-tailed at a significance level of 0.05. We used SAS version 9.4 for all statistical analyses.

Results

A total of 214 patients were enrolled between July 2018 and April 2019. A total of 105 (49%) were randomized to index-guided group, and 108 to unguided group (fig. 2). One patient was excluded from analysis due to nonavailability of data from technical issues. The randomized groups were adequately balanced on all baseline variables (table 1).

The primary and secondary outcomes are reported in table 2 and figure 3, Supplemental Digital Content 2 (http://links.lww.com/ALN/C478), and Supplemental Digital Content 3 (http://links.lww.com/ALN/C479). Randomization to the index-guided group did not reduce AUC (P = 0.715), time-weighted average (P = 0.757), or minutes of MAP less than 65 mmHg (P = 0.328). The estimated median difference (95% CI) of time-weighted average MAP less than 65 mmHg was 0 (–0.03 to 0.04) mmHg, and median difference (95% CI) of AUC-MAP less than 65 mmHg was –1.3 (–12 to 7) mmHg · min, for index-guided minus unguided group. No significant differences were found on secondary outcomes using MAP less than 60 and less than 55 mmHg as thresholds.

Table 3 shows results for intraoperative and postoperative exploratory outcomes. No differences were observed between the guided and unguided groups on exploratory outcomes except for intraoperative crystalloids. The median amount [quartiles] of intraoperative crystalloids in the index-guided group was slightly less than in the unguided group (2.6 l [1.8, 3.5] *vs.* 3.0 l [2.4, 3.7]), with a median difference of –0.4 l (95% CI, –0.7 to –0.1), P = 0.007.

Post Hoc Analysis

Of 832 alerts in the guidance group, 338 (41%) had hypotensive events with a median time (quartiles) to hypotensive event of 4 (1, 9) minutes; of 947 alerts in unguided group, 379 (40%) had hypotensive events with a median time to hypotensive event of 4 (2, 9) minutes.

In the index-guided group, after excluding segments in which actual clinical intervention was "observe" from each patient's MAP data, the medians of time-weighted average, AUC, and minutes of MAP less than 65 mmHg were a relative 57% smaller; median (quartiles) of time-weighted average was 0.06 mmHg (0.01, 0.33), AUC was 14.0 mmHg · min (1.8, 61.6), and minutes was 3.3 (1.0, 9.8; table 4).

The observed agreement between the suggested intervention, using treatment algorithm,[10] and actual intervention by

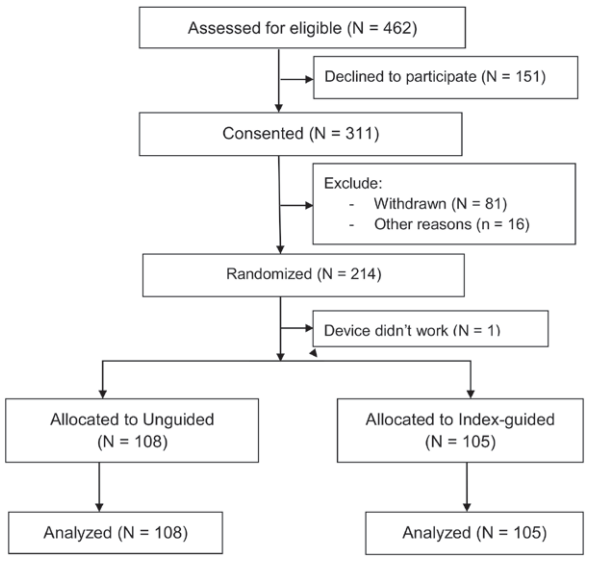

Fig. 2. Trial diagram.

Table 1. Demographic, Baseline, and Surgical Characteristics of the Study Population (N = 213)

Factor	Index-guided* (N = 105)	Unguided† (N = 108)	Absolute Standardized Difference
Demographic and baseline characteristics			
Age, yr	67 ± 10	66 ± 10	0.087
Female	47 (44.8)	43 (39.8)	0.100
Body mass index, kg/m^2	29 ± 9	29 ± 7	0.071
ASA status			0.041
I or II	5 (4.8)	2 (1.9)	
III	81 (77.1)	91 (84.3)	
IV	19 (18.1)	15 (13.9)	
Medical history			
Pulmonary diseases	33 (31.4)	30 (27.8)	0.080
Cardiovascular diseases	74 (70.5)	80 (74.1)	0.080
Neurologic diseases	15 (14.3)	17 (15.7)	0.041
Diabetes	33 (31.7)	34 (31.5)	0.005
Medication history			
Angiotensin-converting enzyme inhibitor	25 (23.8)	21 (19.4)	0.106
β-Blocker	37 (35.2)	40 (37.0)	0.037
Calcium channel blocker	18 (17.1)	19 (17.6)	0.012
Diuretics	26 (24.8)	20 (18.5)	0.152
Antiarrhythmics	4 (3.8)	1 (0.93)	0.191
Statin	44 (41.9)	47 (43.5)	0.033
Nonsteroidal anti-inflammatory drug	49 (46.7)	47 (43.5)	0.063
Surgery type			0.209
Colorectal	14 (13.3)	12 (11.1)	
General	19 (18.1)	26 (24.1)	
Hepatobiliary	19 (18.1)	19 (17.6)	
Orthopedics	7 (6.7)	6 (5.6)	
Other	11 (10.5)	12 (11.1)	
Transplant	7 (6.7)	5 (4.6)	
Urology	11 (10.5)	14 (13.0)	
Vascular	17 (16.2)	14 (13.0)	
Duration of surgery	5.7 ± 2.9	6.2 ± 2.6	0.181
Intraoperative time-weighted average MAP	84.9 ± 7.9	83.4 ± 7.1	0.193

Data are n (%) or mean ± SD. Absolute standardized difference > 0.267 as imbalance.

*Index-guided, group with index guidance. †Unguided, group without index guidance.

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

clinical team is shown in table 5. After a total of 1,527 alerts, 55% (847/1,527) of the times there was no actual intervention, designated "observe." The observed and expected proportions of agreement were 0.53 and 0.30, respectively. The kappa coefficient was estimated as 0.33 (95% CI, 0.29 to 0.36), indicating low-to-moderate agreement beyond that expected by chance between the suggested intervention by treatment algorithm and actual interventions by clinicians.

Discussion

In noncardiac surgical patients who needed arterial catheters, hypotension prediction index guidance did not reduce intraoperative hypotension as measured by time-weighted average, AUC, or minutes less than 65 mmHg. Our results contrast markedly with our expectation that the index guidance would substantially reduce intraoperative hypotension. Potential explanations include inadequacies of the index algorithm, trial design, and clinicians' responses to the alert.

Index values greater than 85, the alert threshold, generally provided a few minutes of warning before hypotension developed: the average was 4 min, but in a quarter of the patients, the warning time was less than 2 min. Clinicians thus had little time to respond before hypotension developed. The index therefore predicted hypotension, but in the absence of treatment, did not prevent hypotension. There were also times when index values and the associated advanced hemodynamic parameters changed rapidly, possibly consequent to surgical manipulation and/or other clinical interventions that are hard to predict and avoid. Nonetheless, a longer predictive time can be obtained by using a lower alert threshold.[9]

Clinicians for both blinded and unblinded patients were asked to avoid MAPs less than 65 mmHg. Under observation, clinicians may well have instituted aggressive hypotension reduction strategies (*e.g.*, Hawthorne effect). Continuous monitoring also reduces hypotension,[15] and specific blood pressure targets presumably do as well. Perhaps consequently, we observed half the hypotension expected from our historical analysis.[10]

To the extent that the predictions are accurate, clinicians will need to intervene quickly to prevent hypotension. The treatment algorithm, previously described,[10] requires interpretation of advanced hemodynamic parameters including stroke volume and dynamic elastance. In practice, both investigators and clinicians found the algorithm difficult to implement, especially since all component measures are dynamic and thus constantly changing. A further difficulty is that the treatment algorithm recommended observation in more than a third of the cases. Furthermore, when fluid was recommended, it proved challenging to infuse a clinically meaningful amount of fluid in the few available minutes before hypotension occurred. Clinicians also declined to intervene in many cases. Consequently, more than half of all the alerts did not provoke interventions. But when clinicians did intervene, hypotension was reduced by 57%. Our results suggest that a simplified treatment algorithm focused on prompt use of vasoactive drugs may reduce hypotension.

In distinct contrast to our finding, a recent single-center randomized controlled trial achieved factor-of-four reduction in hypotension with index guidance in noncardiac surgery patients.[16] The results are notable because investigators included healthier patients, 80% ASA II *versus* 80% ASA III, in our trial. The most obvious explanation is that Wijnberge *et al.* provided routine treatment for hypotension in the control group, which apparently allowed considerable hypotension. We used a different approach and specifically asked clinicians in *both groups* to avoid hypotension to the

Table 2. Comparison of Randomized Groups on Primary and Secondary Outcomes of Intraoperative Hypotension

	Index-guided* (N = 105)	Unguided† (N = 108)	Median Difference‡ (95% CI)	*P* Value§
Primary outcome				
Time-weighted average MAP < 65 mmHg, mmHg	0.14 (0.03, 0.37)	0.14 (0.03, 0.39)	0 (–0.03 to 0.04)	0.757
AUC-MAP < 65 mmHg, mmHg · min	32.7 (6.3, 102.0)	34.2 (8.5, 112.7)	–1.3 (–12 to 7)	0.715
Duration of MAP < 65 mmHg, min	7.7 (2.0, 18.3)	9.3 (2.3, 23.5)	–1 (–3.3 to 1)	0.328
Secondary outcomes				
Time-weighted average MAP < 60 mmHg, mmHg	0.03 (0.00, 0.13)	0.02 (0.00, 0.11)	0 (–0.001 to 0.011)	0.376
AUC-MAP < 60 mmHg, mmHg · min	6.0 (0.33, 28.3)	5.3 (0.00, 29.2)	0 (–0.67, 2.00)	0.610
Duration of MAP < 60 mmHg, min	2.0 (0.33, 7.3)	2.0 (0.00, 7.7)	0 (–0.67 to 0.67)	0.889
Time-weighted average MAP < 55 mmHg, mmHg	0 (0, 0.04)	0 (0, 0.03)	0 (0 to 0)	0.226
AUC MAP < 55 mmHg, mmHg · min	1.00 (0, 7.7)	0.17 (0, 6.7)	0 (0 to 0)	0.302
Duration of MAP < 55 mmHg, min	0.67 (0, 2.3)	0.17 (0, 1.7)	0 (0 to 0)	0.403

Data are presented as median (first quartile, third quartile).

*Index-guided, group with index guidance. †Unguided, group without index guidance. ‡Median difference and 95% CI estimated using Hodges–Lehmann estimator. §*P* value corresponded to Wilcoxon rank sum test.

AUC, area under the receiver operating characteristics curve; MAP, mean arterial pressure.

extent possible. Our results thus represent the added benefit of index guidance on hypotension reduction, within the constraints of our treatment algorithm.

Patients from only two hospitals in a single institution were included, and we excluded patients with certain cardiac conditions, which limits generalizability. The index should be evaluated in different patient populations and practice settings to confirm utility in clinical care. But given our equivocal results, it seems unlikely that including some especially sick patients would change our conclusions. During the screening and consenting process, we used available information to ascertain ASA physical status and included only those we believed to be physical status III or IV. However, the anesthesiologist in charge of the case determined the ASA status of record, which sometimes differed from the investigators' designation. Consequently, a few enrolled patients had recorded ASA physical status scores of I or II.

Another limitation of our trial is that the treatment algorithm we used has been published but not validated. Instead, it was largely based on expert clinical opinion and available evidence. Finally, clinicians may have presumed that interventions such as low-dose vasopressors are harmful, although there is no evidence to support that assumption.[17]

Interpretation of complex hemodynamic information can be challenging, and trained research team members were available to help clinicians follow the treatment protocol. But we explicitly did not require clinicians to comply with treatment algorithm recommendations, instead letting them use clinical judgment. Mistrust in

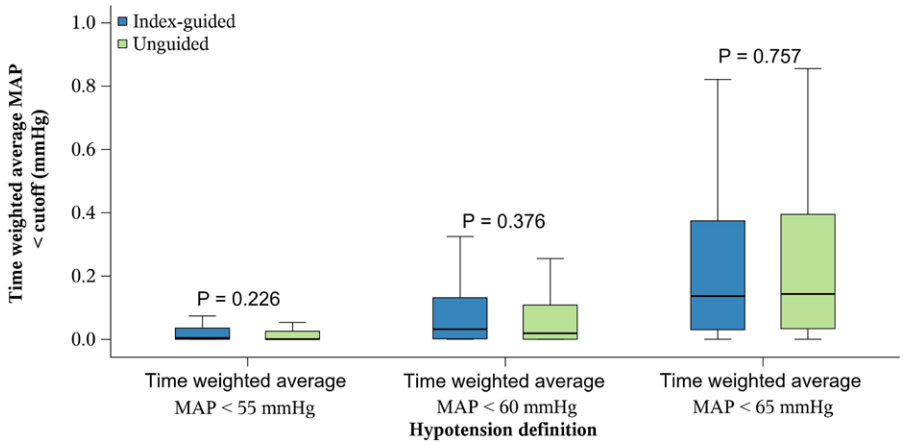

Fig. 3. Distribution of time-weighted average mean arterial pressure (MAP) hypotension by randomized monitoring type at various MAP thresholds.

Table 3. Comparison of Randomized Groups on Intraoperative and Postoperative Exploratory Outcomes

Outcome	Index-guided* (N = 105)	Unguided† (N = 108)	Estimation (95% CI)	*P* Value‡
Intraoperative			Median difference	
Crystalloids, l	2.6 (1.8, 3.5)	3.0 (2.4, 3.75)	–0.4 (–0.7 to –0.1)	0.007
Colloids, l	0.5 (0, 1)	0.5 (0, 1)	0 (–0.25 to 0.0001)	0.516
Estimated blood loss, ml	200 (50, 400)	200 (100, 375)	–10 (–50 to 30)	0.402
Urine output, ml	365 (230, 635)	407 (210, 667)	–5 (–100 to 75)	0.843
Phenylephrine, mg	1.53 (0.45, 7.87)	2.62 (0.51, 8.12)	–0.15 (–0.85 to 0.35)	0.535
			Relative risk	
Received transfusion	27 (25.7)	21 (19.4)	1.32 (0.80 to 2.19)	0.274
Phenylephrine use	98 (93.3)	102 (94.4)	1.00 (0.90 to 1.10)	0.735
Norepinephrine	4 (3.8)	4 (3.7)	1.00 (0.30 to 4.00)	> 0.999
Ephedrine use	8 (7.6)	3 (2.8)	2.70 (0.70 to 10.10)	0.110
Vasopressin use	2 (1.9)	2 (1.9)	1.00 (0.10 to 7.10)	> 0.999
			Mean difference	
Cardiac output	5.5 ± 1.4	5.8 ± 1.5	–0.29 (–0.69 to 0.098)	0.141
Cardiac index	2.9 ± 0.70	2.9 ± 0.69	–0.09 (–0.28 to 0.097)	0.340
Stroke volume	77.8 ± 19.8	80.2 ± 19.1	–2.46 (–7.72 to 2.79)	0.357
Stroke volume variation	10.1 ± 4.1	9.8 ± 3.7	0.35 (–0.71 to 1.41)	0.519
Postoperative			Mean difference	
Quality of Recovery score§	103 ± 27¶	108 ± 22‖	–4.5 (–11.6 to 2.6)	0.210
			Relative risk	
A composite of in-hospital death, stroke, and myocardial injury	7 (6.7)	12 (11.1)	0.60 (0.20 to 1.50)	0.255
In-hospital death	0 (0.0)	1 (0.93)		
Stroke	5 (4.8)	8 (7.4)		
Myocardial injury	2 (2.8)	5 (6.7)		
Acute kidney injury	15 (14.3)	20 (18.5)	0.80 (0.40 to 1.40)	0.405
Patients with postoperative morbidity survey-defined morbidity	68 (66.7)**	79 (75.2)**	0.90 (0.70 to 1.10)	0.174
Pulmonary	38 (37.3)	50 (47.6)	0.7 (0.6, 1.1)	0.132
Infectious	22 (21.6)	34 (32.4)	0.7 (0.4, 1.1)	0.080
Renal	17 (16.7)	14 (13.3)	1.2 (0.6, 2.4)	0.502
Gastrointestinal	33 (32.4)	27 (25.7)	1.2 (0.8, 1.9)	0.293
Cardiovascular	12 (11.8)	20 (19.0)	0.6 (0.3, 1.2)	0.147
Neurologic	5 (4.9)	7 (6.7)	0.7 (0.2, 2.2)	0.587
Wound	13 (12.7)	11 (10.5)	1.2 (0.5, 2.6)	0.610
Hematologic	0 (0.0)	1 (0.9)	NA	> 0.999
Pain	10 (9.8)	8 (7.6)	1.3 (0.5, 3.1)	0.577
Hospital readmission within 30 days	19 (18.1)	18 (16.7)	1.10 (0.60 to 1.90)	0.783
			Hazard ratio	
Length of hospital stay	6 (3, 9)	6 (4, 8)	0.97 (0.74 to 1.27)	0.814

Data are n (%), mean ± SD, or median (interquartile range). Myocardial injury means myocardial injury after noncardiac surgery. NA indicates nonestimable due to 0 frequency.

*Index-guided, group with index guidance. †Unguided, group without index guidance. ‡Wilcoxon rank sum test for skewed data, *t* test for normal distributed data, chi-square test for categorical data, and log rank test for time-to-event data (*i.e.*, length of hospital stay), as appropriate. Median difference and 95% CI estimated using Hodges–Lehmann estimator. §Score range from 0 to 150. Higher scores indicate better recovery. ¶13, ‖14, and **3 missing data points.

unfamiliar technology may also have contributed to lack of interventions despite alert. For example, a randomized trial of alerts for Triple Low episodes (low Bispectral Index, low systolic pressure, and low anesthetic concentration) failed because clinicians largely ignored the warnings.[18] Clear treatment guidance and education focused on compliance should be integral to future trials using index guidance.

In summary, the index predicted hypotension, but the use of index failed to reduce hypotension. When analysis was restricted to episodes in which clinicians intervened, hypotension was halved, and suggesting that prompt treatment may have helped. Our results suggest that the treatment algorithm used in this pilot trial was excessively complicated and too often recommended no intervention or fluid administration, which could not be accomplished fast enough to prevent hypotension. The planned full trial will therefore use a lower alert threshold and a simpler treatment algorithm that emphasizes prompt treatment.

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Competing Interests

Drs. Maheshwari and Sessler are consultants for Edwards Lifesciences (Irvine, California).

Table 4. Hypotension Prediction Index Patients: Amount of Hypotension in "Full Case" *versus* "Intervened Only"

Outcome	Index-guided (Full Case)* (N = 105)	Index-guided (Intervened Only)† (N = 105)
< 65 mmHg		
Time-weighted average MAP < 65 mmHg, mmHg	0.14 (0.03, 0.37)	0.06 (0.01, 0.33)
AUC-MAP < 65 mmHg, mmHg · min	32.7 (6.3, 102.0)	14.0 (1.8, 61.6)
Duration of MAP < 65 mmHg, min	7.7 (2.0, 18.3)	3.3 (1.0, 9.8)
< 60 mmHg		
Time-weighted average MAP < 60 mmHg, mmHg	0.03 (0.00, 0.10)	0.0 (0.0, 0.11)
AUC-MAP < 60 mmHg, mmHg · min	6.0 (0.30, 28.30)	0.0 (0.0, 19.6)
Duration of MAP < 60 mmHg, min	2.0 (0.30, 7.30)	0.0 (0.0, 4.3)
< 55 mmHg		
Time-weighted average MAP < 55 mmHg, mmHg	0.00 (0.00, 0.04)	0.0 (0.0, 0.01)
AUC-MAP < 55 mmHg, mmHg · min	1.0 (0.00, 7.70)	0.0 (0.0, 3.5)
Duration of MAP < 55 mmHg, min	0.70 (0.00, 2.30)	0.0(0.0, 1.3)

Data are median (quartiles). Index-guided means group with index guidance.

*Full case: using all data during case, independent of clinician response. †Intervened only: For this column we removed data from a patient's intraoperative MAP corresponding to "observe" segments, *i.e.*, periods in which the actual intervention by clinician was "observe." Such periods extended to the time of the next intervention or 10 min, whichever came first. Any hypotension that happened during an "observe" segment was thus not counted, due to no delivery of interventions after an alert. This column also removes initial segments before intervention algorithm per hypotension prediction index guidance was started.

AUC, area under the receiver operating characteristics curve; MAP, mean arterial pressure.

Table 5. Agreement between Suggested Intervention Using Treatment Algorithm[13] and Actual Intervention by Clinical Team

Index > 85	Actual Intervention						
Suggested Intervention	1: Fluid + Vasopressor	2: Fluid + Inotrope	3: Fluid	4: Vasopressor	5: Inotrope	6: Observe	Total
1: Fluid + vasopressor	52	1	11	31	1	58	154
2: Fluid + inotrope	13	13	10	24	1	25	86
3: Fluid	20	2	75	33	3	82	215
4: Vasopressor	4	0	21	182	17	164	388
5: Inotrope	4	0	8	35	9	45	101
6: Observe	7	0	24	70	9	473	583
Total	100	16	149	375	40	847	1,527

The kappa coefficient has 0.33 (95% CI, 0.29 to 0.36), indicating slight agreement beyond chance between the suggested and actual interventions. The observed proportion of agreement was 0.53 and the expected proportion of agreement was 0.30.

Reproducible Science

Full protocol available at: MAHESHK@ccf.org. Raw data available at: MAHESHK@ccf.org.

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