Ability of an Arterial Waveform Analysis–Derived Hypotension Prediction Index to Predict Future Hypotensive Events in Surgical Patients

Simon James Davies, MD, PhD,* Simon Tilma Vistisen, PhD,† Zhongping Jian, PhD,‡ Feras Hatib, PhD,‡ and Thomas W. L. Scheeren, PhD§

BACKGROUND: Intraoperative hypotension is associated with worse perioperative outcomes for patients undergoing major noncardiac surgery. The Hypotension Prediction Index is a unitless number that is derived from an arterial pressure waveform trace, and as the number increases, the risk of hypotension occurring in the near future increases. We investigated the diagnostic ability of the Hypotension Prediction Index in predicting impending intraoperative hypotension in comparison to other commonly collected perioperative hemodynamic variables.

METHODS: This is a 2-center retrospective analysis of patients undergoing major surgery. Data were downloaded and analyzed from the Edwards Lifesciences EV1000 platform. Receiver operating characteristic curves were constructed for the Hypotension Prediction Index and other hemodynamic variables as well as event rates and time to event.

RESULTS: Two hundred fifty-five patients undergoing major surgery were included in the analysis yielding 292,025 data points. The Hypotension Prediction Index predicted hypotension with a sensitivity and specificity of 85.8% (95% CI, 85.8%–85.9%) and 85.8% (95% CI, 85.8%–85.9%) 5 minutes before a hypotensive event (area under the curve, 0.926 [95% CI, 0.925–0.926]); 81.7% (95% CI, 81.6%–81.8%) and 81.7% (95% CI, 81.6%–81.8%) 10 minutes before a hypotensive event (area under the curve, 0.895 [95% CI, 0.894–0.895]); and 80.6% (95% CI, 80.5%–80.7%) and 80.6% (95% CI, 80.5%–80.7%) 15 minutes before a hypotensive event (area under the curve, 0.879 [95% CI, 0.879–0.880]). The Hypotension Prediction Index performed superior to all other measured hemodynamic variables including mean arterial pressure and change in mean arterial pressure over a 3-minute window.

CONCLUSIONS: The Hypotension Prediction Index provides an accurate real time and continuous prediction of impending intraoperative hypotension before its occurrence and has superior predictive ability than the commonly measured perioperative hemodynamic variables. (Anesth Analg XXX;XXX:00–00)

KEY POINTS

- **Question:** Can an arterial waveform–derived algorithm predict hypotension before it occurs?
- **Findings:** The Hypotension Prediction Index predicts hypotension up to 15 minutes before it occurs with good sensitivity and specificity.
- **Meaning:** The algorithm could be potentially used to decrease the incidence of perioperative hypotension.

Because there is no universal definition of intraoperative hypotension, its reported incidence varies with the chosen threshold from 12% to 94%.[1,2] Risk factors for intraoperative hypotension include emergency surgery, age, preinduction hypotension, neuraxial blocks, male sex, and American Society of Anesthesiologists class IV.[3]

Intraoperative hypotension has been associated with acute kidney injury and myocardial injury after noncardiac surgery.[4,5] It appears it is the cumulative time spent in hypotension that increases the risk of harm to patients, and this has implications as even relatively short episodes of hypotension that are treated promptly can over time reach accumulated hypotension time associated with increased injury rates. To reduce the incidence of intraoperative hypotension, both in absolute and cumulative terms, it would be intriguing if a hypotensive event could be predicted allowing clinicians to move from a reactive state of treating a hypotensive event after it has occurred to a proactive state of treating it before it is going to happen. This would be a major step forward because it expands the diagnostic and monitoring abilities currently available in operating rooms, which fail to predict hypotension at an early stage.

From the *Department of Anaesthesia, Critical Care and Perioperative Medicine, York Teaching Hospital National Health Service Foundation Trust, York, United Kingdom; †Department of Clinical Medicine, Aarhus University, Aarhus, Denmark; ‡Edwards Lifesciences Ltd, Irvine, California; and §Department of Anaesthesiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.

Accepted for publication January 28, 2019.

Funding: None.

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-analgesia.org).

Reprints will not be available from the authors.

S. T. Vistisen's ORCID iD: https://orcid.org/0000-0002-1297-1459. T. W. L. Scheeren's ORCID iD: https://orcid.org/0000-0002-9184-4190.

Address correspondence to Simon James Davies, MD, PhD, Department of Anaesthesia, Critical Care and Perioperative Medicine, York Teaching Hospital National Health Service Foundation Trust, Wiggington Rd, York YO31 8HE, United Kingdom. Address e-mail to simon.davies@york.nhs.uk.

DOI: 10.1213/ANE.0000000000004121

The Hypotension Prediction Index is a unitless number that ranges from 1 to 100, and as the number increases, the risk of an event occurring in the future increases. The event is hypotension defined as a mean arterial pressure (MAP) of <65 mmHg occurring for >1 minute. The derivation of the algorithm has recently been described.[6] Briefly, the Hypotension Prediction Index was developed using machine learning methods and is a data-driven model developed from over 200,000 hypotensive patient events and it predicts upcoming hypotensive events based on features of the arterial pressure waveform.

The purpose of this study was to assess the diagnostic ability of the Hypotension Prediction Index algorithm and other hemodynamic variables in predicting impending hypotension.

METHODS

This is a retrospective analysis of prospectively gathered anonymized data. York Teaching Hospital Foundation Trust sponsored the study, which was approved by the UK Health Research Authority (integrated research application system no. 247048). The requirement for written informed consent was waived by the Health Research Authority. This manuscript adheres to the Enhancing the QUality and Transparency Of health Research guidelines.[7]

Data were analyzed from subjects who underwent perioperative monitoring on the Edwards Lifesciences EV1000 monitoring system (Edwards Lifesciences, Irvine, CA) containing the Hypotension Prediction Index software (Edwards Lifesciences, Irvine, CA) from 2 institutions (York Teaching Hospitals National Health Service Foundation Trust and University Medical Centre Groningen). Data were collected from November 2016 to December 2017.

Eligibility was determined by subjects undergoing major surgery (major abdominal, vascular, or off-pump coronary artery bypass surgery) requiring arterial cannulation for blood pressure and/or cardiac output (CO) measuring and who had intact complete data sets available for analysis.

Anesthetic technique was solely at the discretion of the treating anesthetist, and all patients received goal-directed fluid therapy as per the institutions' policies which was to maintain a stroke volume variation (SVV) of ≤12% by administering 250 mL boluses of fluid when SVV was >12%, or in those in whom SVV was not a valid variable, then SV was maximized using repeated 250 mL fluid boluses until a SV rise in excess of 10% was no longer seen. Subjects received a mixture of both colloid and crystalloid fluid boli.

All data computed by the Edwards Lifesciences' arterial pressure based cardiac output algorithm were downloaded from the EV1000 monitors as follows: the Hypotension Prediction Index, CO, MAP, SV, SVV, heart rate (HR), pulse pressure, pulse pressure variation, and systemic vascular resistance. All downloaded data consisted of 20-second interval samples. In addition, arterial blood pressure waveforms collected with a sampling rate of 100 Hz were downloaded from the EV1000 monitors and processed to compute the shock index,[8] modified shock index, contractility[9,10] (dP/dt_{max}), and dynamic arterial elastance[11,12] for 20 seconds between each time point. Dynamic arterial elastance was calculated as pulse pressure variation/SVV. In the EV1000 monitor, poor arterial waveforms (eg, those resulted from line flushing, flat lines, significantly damped waveforms, and other waveform artifacts) are detected by the arterial pulse contour algorithm and excluded from the analysis. Details on how the Hypotension Prediction Index algorithm was derived are included in Supplemental Digital Content 1, File 1, http://links.lww.com/AA/C772, and explained in detail elsewhere.[6]

Statistical Analysis

Descriptive statistics are presented as mean (SD) for normally distributed continuous data, minimum–maximum, or median (25th–75th percentiles) for nonnormally distributed data, and valid n if data are missing. Categorical data are presented as n (%).

The data set was analyzed in its entirety. The total number of hypotensive events was calculated and analyzed in terms of absolute duration, area under the threshold of 65 mmHg, and time-weighted average of area under the threshold calculated as area under the threshold/duration of monitoring.[1]

Receiver operating characteristic analysis was used to evaluate the performance of the Hypotension Prediction Index in predicting hypotension. The optimal cutoff value was defined to be the threshold value that minimizes the difference between the sensitivity and specificity as both were considered equally important. A hypotensive event was defined as a MAP <65 mmHg for ≥1 minute. Receiver operating characteristic analysis was used to evaluate the performance of the change of MAP (ΔMAP) to predict hypotension as well as MAP, CO, SV, pulse pressure, HR, SVV, pulse pressure variation, and systemic vascular resistance. Delta variables were calculated as the difference in 2 measurements that are 3 minutes apart. ΔMAP analysis was performed for the entire range of MAP that occurred, and also separately in the ranges of 65–75, 75–85, and 85–95 mmHg because it was hypothesized that changes in MAP may be more predictive of intraoperative hypotension as the threshold defining hypotension was approached.

The hypotensive event rate was calculated for a given the Hypotension Prediction Index and the time to the event occurrence.

There are a number of sources of potential bias: first, due to the retrospective nature of the data analysis, we are unable to determine if interventions occurred to treat hypotension; second, clinicians may not have been blinded to the Hypotension Prediction Index; and third, we are unable to account for hypotension due to external factors (eg, unclamping of arterial vessels or position change of patients). All of the above would lead to an increased false-negative rate for the prediction index and hence may lower the predictive ability of the Hypotension Prediction Index in the analysis. Data segments containing clinical interventions that prevented hypotension were excluded from the event rate and time to event analysis. Such interventions were not registered but defined by the collected data as a MAP rise of >5 mmHg in 20 seconds (mostly caused by vasopressor or inotropic injections) or >8 mmHg in 2 minutes (change in vasopressor or inotropic infusion rate or fluid bolus) when the MAP was <75 mmHg.

The repeated measure from same subjects was compensated using the bootstrapping method in all the statistical analysis[13] where bootstrapping was performed as follows: 255 patients were randomly chosen from the total 255 patients with replacement. This process was repeated 2000 times from which the standard error was calculated. The bootstrap CI was calculated as a 95% asymptotic CI because the distribution of the standardized statistic, Z_β, was approximately normal.

An a priori sample size calculation was not performed. Observed CIs are relatively narrow suggesting a sufficient precision of the estimates at the available sample size for the aims of this study.

All statistics were performed with MATLAB (version R2014a; The Mathworks Inc, Natick, MA).

RESULTS

Two hundred fifty-five patients (78 female and 177 male) with a mean age of 68 years (13 years) were included in the analysis yielding 292,025 data points. The median monitoring time per patient was 204 minutes (130–293 minutes), and 221 of 255 subjects (86.7%) had at least ≥1 hypotensive event defined as a MAP <65 mmHg for >1 minute. In total, 2292 hypotensive events were detected and the median number of events per patient was 4 (1–9) with a median duration of 2 minutes (1–5 minutes) per event. The median cumulative duration of hypotension per patient was 11 minutes (3–38 minutes) (6% [1%–19%] of total monitoring time) with a median area under the threshold of 65 mmHg of 56 mmHg min (17–246 mmHg min) and a time-weighted average area under the threshold of 0.3 mmHg (0.1–1.1 mmHg).

Prediction of Hypotension 5 Minutes Before the Event

Receiver operating characteristic curves for the ability of the Hypotension Prediction Index to predict hypotension at 5 minutes from the measurement point are shown in Figure 1, and area under the curve, sensitivity, specificity, positive predictive value, negative predictive value, and optimal cutoff values are shown in Supplemental Digital Content 2, Table 1, http://links.lww.com/AA/C773. The area under the curve for the prediction of hypotension 5 minutes before the event for the Hypotension Prediction Index was 0.926 (95% CI, 0.925–0.926; sensitivity, 86%; specificity, 86%) with a positive predictive value of 89% and a negative predictive value of 82%.

Area under the curve, sensitivity, specificity, positive predictive value, negative predictive value, and optimal cutoff for static hemodynamic variables are shown in Supplement Digital Content 3, Table 2, http://links.lww.com/AA/C774, and Figure 2. The area under the curve for static variables predicting hypotension 5 minutes before the event was MAP 0.807 (95% CI, 0.807–0.808), pulse pressure 0.647 (95% CI, 0.646–0.648), SV 0.538 (95% CI, 0.536–0.539), HR 0.530 (95% CI, 0.529–0.531), and for SVV 0.526 (95% CI, 0.525–0.527).

ΔMAP changes across the entire range had an area under the curve of 0.549 (95% CI, 0.548–0.550) for predicting hypotension at 5 minutes. Analysis of ΔMAP in various MAP ranges is shown in Supplemental Digital Content 2, Table 1, http://links.lww.com/AA/C773. The predictive ability of other δ variables is shown in Supplemental Digital Content 4, Table 3, http://links.lww.com/AA/C775, and includes change in pulse pressure 0.539 (95% CI, 0.538–0.540); change in SV 0.515 (95% CI, 0.515–0.516); change in HR 0.512 (95% CI, 0.512–0.513), and for change in SVV 0.510 (95% CI, 0.509–0.510).

Prediction of Hypotension 10 Minutes Before the Event

Receiver operating characteristic curves for the ability of the Hypotension Prediction Index to predict hypotension at 10

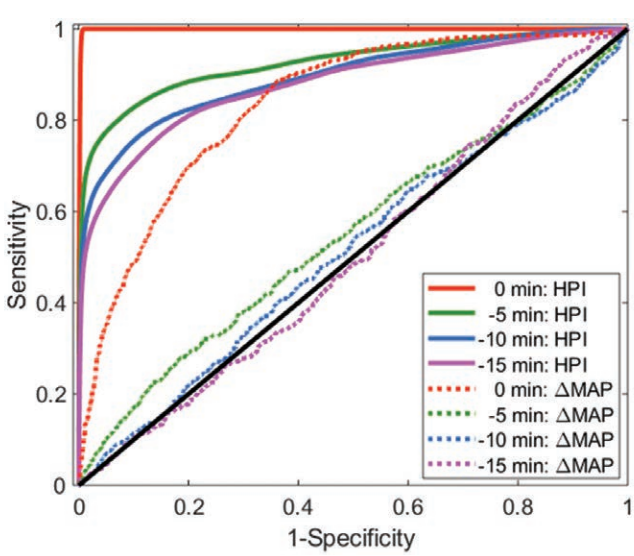

Figure 1. Receiver operating characteristic curves for the HPI and ΔMAP over the previous 3 min for predicting hypotension at the time of event (0 min) and 5, 10, and 15 min before its occurrence. HPI indicates Hypotension Prediction Index; ΔMAP, change in mean arterial pressure.

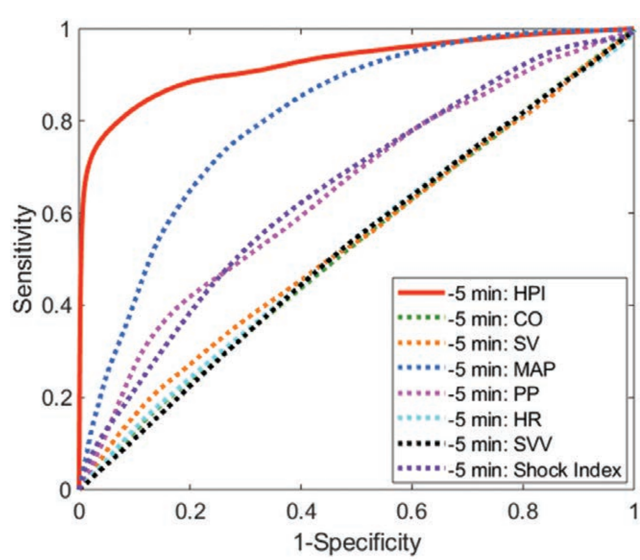

Figure 2. Receiver operating characteristic curves for HPI, CO, SV, MAP, PP, HR, SVV, and the shock index for prediction hypotension 5 min before the event. CO indicates cardiac output; HPI, Hypotension Prediction Index; HR, heart rate; MAP, mean arterial pressure; PP, pulse pressure; SV, stroke volume; SVV, stroke volume variation.

minutes from the measurement point are shown in Figure 1, and area under the curve, sensitivity, specificity, positive predictive value, negative predictive value, and optimal cutoff are shown in Supplemental Digital Content 2, Table 1, http://links.lww.com/AA/C773. The area under the curve for the prediction of hypotension 10 minutes before the event for the Hypotension Prediction Index was 0.895 (95% CI, 0.894–0.895; sensitivity, 82%; specificity, 82%) with a positive predictive value of 79% and a negative predictive value of 83%.

Area under the curve, sensitivity, specificity, positive predictive value, negative predictive value, and optimal cutoff for static hemodynamic variables are shown in Supplement Digital Content 3, Table 2, http://links.lww.com/AA/C774 and Figure 3. The area under the curve for static variables predicting hypotension 10 minutes before the event was as follows: MAP 0.754 (95% CI, 0.753–0.755); pulse pressure 0.622 (95% CI, 0.621–0.623), SV 0.531 (95% CI, 0.530–0.532), HR 0.529 (95% CI, 0.528–0.530), and SVV 0.528 (95% CI, 0.528–0.530).

ΔMAP changes across the entire range had an area under the curve of 0.515 (95% CI, 0.515–0.516) for predicting hypotension at 10 minutes. Analysis of ΔMAP in various threshold ranges is shown in Supplemental Digital Content 2, Table 1, http://links.lww.com/AA/C773. The predictive ability of other δ variables is shown in Supplemental Digital Content 4, Table 3, http://links.lww.com/AA/C775, and includes change in pulse pressure 0.514 (95% CI, 0.514–0.515), change in SV 0.513 (95% CI, 0.513–0.513), change in HR 0.511 (95% CI, 0.511–0.511), and for change in SVV 0.518 (95% CI, 0.517–0.518).

Prediction of Hypotension 15 Minutes Before the Event

Receiver operating characteristic curves for the ability of the Hypotension Prediction Index to predict hypotension at 15 minutes from the measurement point are shown in Figure 1, and area under the curve, sensitivity, specificity, positive predictive value, negative predictive value, and optimal cutoff are shown in Supplemental Digital Content 2, Table 1, http://links.lww.com/AA/C773. The area under the curve for the prediction of hypotension 15 minutes before the event for the Hypotension Prediction Index was 0.879 (95% CI, 0.879–0.880; sensitivity, 81%; specificity, 81%), with a positive predictive value of 73% and a negative predictive value of 87%.

Area under the curve, sensitivity, specificity, positive predictive value, negative predictive value, and optimal cutoff for static hemodynamic variables are shown in Supplement Digital Content 3, Table 2, http://links.lww.com/AA/C774, and Figure 4. The area under the curve for static variables predicting hypotension 15 minutes before the event was MAP 0.722 (95% CI, 0.721–0.723); pulse pressure 0.612 (95% CI, 0.610–0.613), SV 0.533 (95% CI, 0.532–0.534), HR 0.531 (95% CI, 0.530–0.532), and SVV 0.543 (95% CI, 0.542–0.545).

ΔMAP changes across the entire range had an area under the curve of 0.516 (95% CI, 0.515–0.516) for predicting hypotension at 15 minutes. Analysis of ΔMAP in various threshold ranges is shown in Supplemental Digital Content 2, Table 1, http://links.lww.com/AA/C773. The predictive ability of other δ variables is shown in Supplemental Digital Content 4, Table 3, http://links.lww.com/AA/C775, and includes change in pulse pressure 0.516 (95% CI, 0.516–0.517), change in SV 0.519 (95% CI, 0.518–0.520), change in HR 0.514 (95% CI, 0.514–0.515), and change in SVV 0.525 (95% CI, 0.524–0.525).

The incidence of hypotension and the time to a hypotensive event in relation to the Hypotension Prediction Index are shown in the Table, and additional analysis of this relationship is shown in Supplemental Digital Content 1, File 1, http://links.lww.com/AA/C772. As the Hypotension Prediction Index increased, the incidence of intraoperative hypotension increased and the median time to the actual hypotensive event decreased.

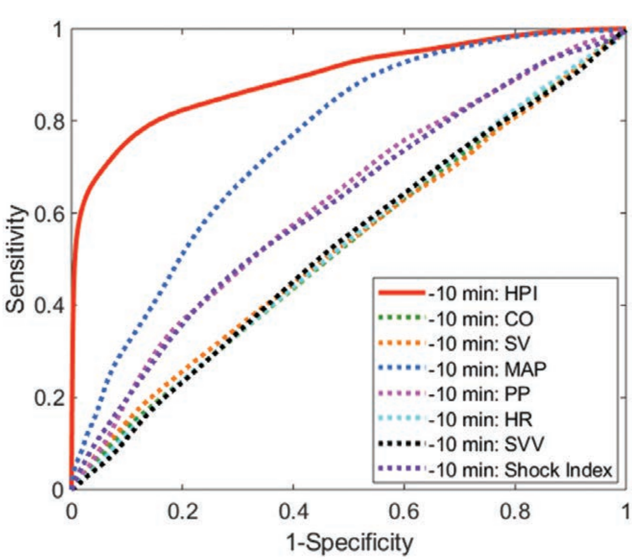

Figure 3. Receiver operating characteristic curves for HPI, CO, SV, MAP, PP, HR, SVV, and the shock index for prediction hypotension 10 min before the event. CO indicates cardiac output; HPI, Hypotension Prediction Index; HR, heart rate; MAP, mean arterial pressure; PP, pulse pressure; SV, stroke volume; SVV, stroke volume variation.

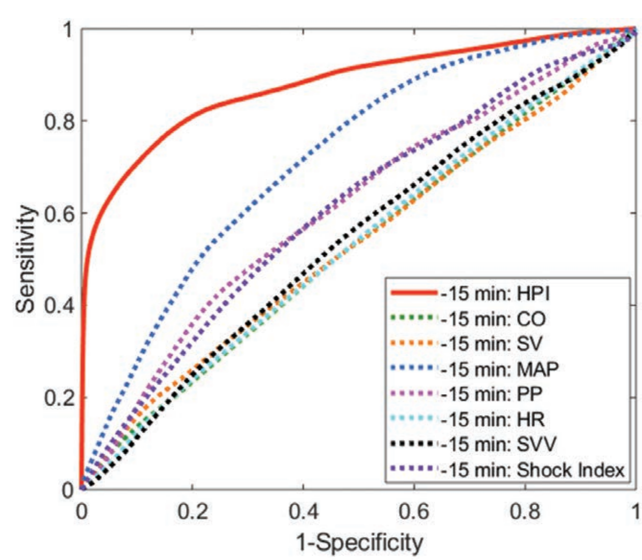

Figure 4. Receiver operating characteristic curves for HPI, CO, SV, MAP, PP, HR, SVV, and the shock index for prediction hypotension 15 min before the event. CO indicates cardiac output; HPI, Hypotension Prediction Index; HR, heart rate; MAP, mean arterial pressure; PP, pulse pressure; SV, stroke volume; SVV, stroke volume variation.

Table. Incidence of Hypotension and Time to Event in Relation to Different Thresholds of the Hypotension Prediction Index

Hypotension Prediction Index	Event Rate (95% CI) (%)	Median Time to Event (95% CI) (min)	25th Percentile Time to Event (95% CI) (min)	75th Percentile Time to Event (95% CI) (min)	10th Percentile Time to Event (95% CI) (min)	90th Percentile Time to Event (95% CI) (min)	No. of Samples
0–9	20.9 (20.8–21.1)	9.38 (9.36–9.39)	5.59 (5.58–5.60)	13.86 (13.84–13.87)	3.40 (3.39–3.41)	17.25 (17.24–17.26)	6060/29,718
10–19	27.2 (27.1–27.4)	9.24 (9.22–9.25)	5.19 (5.18–5.20)	14.01 (14.00–14.02)	2.89 (2.88–2.90)	17.57 (17.56–17.58)	6307/23,362
20–29	32.8 (32.7–33.0)	8.76 (8.75–8.78)	4.93 (4.92–4.94)	13.52 (13.51–13.53)	2.49 (2.48–2.50)	17.17 (17.16–17.17)	8666/26,605
30–39	43.9 (43.8–44.1)	7.45 (7.44–7.46)	3.86 (3.85–3.87)	12.43 (12.42–12.45)	1.74 (1.73–1.75)	16.66 (16.65–16.67)	13,784/31,543
40–49	51.9 (51.7–52.1)	6.30 (6.28–6.31)	2.85 (2.84–2.86)	11.55 (11.53–11.57)	1.11 (1.11–1.12)	15.97 (15.96–15.98)	10,659/20,616
50–59	56.4 (56.2–56.6)	5.52 (5.50–5.54)	2.27 (2.26–2.28)	11.02 (11.00–11.05)	0.77 (0.76–0.77)	15.71 (15.70–15.73)	9883/17,659
60–69	64.7 (64.5–64.9)	4.97 (4.95–4.99)	1.87 (1.86–1.88)	10.12 (10.10–10.15)	0.49 (0.48–0.50)	15.15 (15.14–15.17)	11,622/18,080
70–79	69.6 (69.5–69.8)	4.19 (4.17–4.20)	1.45 (1.44–1.46)	9.05 (9.02–9.07)	0.22 (0.22–0.23)	14.48 (14.46–14.50)	10,535/15,178
80–89	74.2 (74.1–74.4)	3.74 (3.73–3.75)	1.10 (1.10–1.11)	8.44 (8.42–8.46)	0.01 (0.00–0.01)	14.06 (14.03–14.08)	12,084/16,312
90–99	86.3 (86.2–86.4)	2.23 (2.22–2.23)	0.68 (0.68–0.69)	6.07 (6.06–6.09)	0 (0–0)	11.57 (11.54–11.59)	50,755/58,841
100	100 (100–100)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	31,951/31,951

DISCUSSION

This study shows that the proprietary Hypotension Prediction Index algorithm can predict a hypotensive event, defined as a MAP of <65 mmHg for ≥1 minute, up to 15 minutes before the event. In addition, the Hypotension Prediction Index is superior in predicting intraoperative hypotension compared to static hemodynamic variables that are commonly used by clinicians as well as the dynamic changes in these variables over time.

The incidence of hypotension in a surgical population clearly depends on the definition of hypotension that is accepted[2]; however, recent literature has suggested that 65 mmHg is a critical threshold below which the risk of acute kidney injury, myocardial injury, and mortality increase.[4] All patients in this study received goal-directed fluid therapy due to it being standard practice within the 2 institutions; however, despite this, 98.2% of patients had a hypotensive event and the time weighted average was 0.8 mmHg, which is considerably higher than the 0.05 and 0.11 mmHg reported by Maheshwari et al[14] in patients that had either continuous or intermittent blood pressure monitoring in place. Despite receiving goal-directed fluid therapy, a significant hypotensive burden was accumulated in this cohort, which if the association between hypotension and adverse outcome is a causal relation would suggest that fluid optimization alone is not a sufficient therapy for patients undergoing major surgery, and that blood pressure control should be included in any perioperative treatment algorithm. The reasons for the higher incidence and burden of hypotension are unclear. This cohort included patients undergoing off-pump coronary artery bypass grafting; however, exclusion of these patients did not decrease the incidence of hypotension but did reduce the time-weighted average to 0.6 mmHg, still higher than reported in the previous work. In addition, the monitoring time was longer in this cohort as a number of patients continued being monitored into the postoperative period, and it may be that that there was significant hypotension occurring in this period.

As the Hypotension Prediction Index increases, the actual incidence of hypotension occurring in the future increases and the time to that event decreases. Even though with a low Hypotension Prediction Index (0–9) we showed a future hypotension rate of 20.9%, in this group, the Hypotension Prediction Index would increase as hypotension approached; however, a low Hypotension Prediction Index signals that for the majority of subjects' hypotensive events are unlikely to occur in the short term.

The predictive ability of the Hypotension Prediction Index algorithm in this study is similar to that seen in the derivation and validation cohorts of the algorithm development set that has recently been published.[6] The internal validation set had relatively few patients undergoing surgery as it was predominately intensive care patients; however, the external validation set was purely subjects undergoing surgery and our data more closely resemble this cohort both for the Hypotension Prediction Index and ΔMAP over 3 minutes. This study differs from the one by Hatib et al[6] in that we compared the predictive ability of the Hypotension Prediction Index to other commonly measured variables such as SV and HR among others in patients who received goal-directed fluid therapy as a standard of care. We also included the gray zone area of 65–75 mmHg that was not previously analyzed and have not excluded interventions to treat hypotension or external factors (eg, position change in the receiver operating characteristic analysis) giving a "real-world" analysis of the Hypotension Prediction Index in the clinical setting. In addition, we have analyzed the effect of ΔMAP over differing ranges to see if this impacted its predictive ability.

The predictive ability of ΔMAP to detect impending hypotension was analyzed in various incremental MAP ranges. The premise was that a ΔMAP, for example, of 5 mmHg over the previous 3 minutes would be more predictive of impending hypotension if the subject was closer to the hypotensive threshold (MAP range, 65–75 mmHg) than if they were further away (MAP range, 85–95 mmHg). ΔMAP in the zone closest to the definition of hypotension was no more predictive than those in the higher MAP range and appeared to perform worse. One reason for this observation might be that in the algorithm development the model defined subjects as being hypotensive with a MAP <65 mmHg and nonhypotensive with a MAP >75 mmHg to have separable and mutually exclusive labels. The data between these 2 binary classifications were not analyzed in the model development. The optimal cutoff values for ΔMAP predicting hypotension events are small in the range of 0.4–3.1 mmHg when >5 minutes from a hypotensive event and are within the measurement error of most systems making clinical utility low.

Given that even dynamic changes in MAP are poorly predictive of impending hypotension, it is not surprising that the static single measurements as well as the dynamic δ measurements of other commonly measured hemodynamic variables also provide little if any predictive ability. The Hypotension Prediction Index algorithm is based on detection of physiological signatures in arterial pressure waveforms (loss of complexity) caused by the weakening of the cardiovascular compensatory mechanisms that occur before hypotension. These changes are multivariate including features related to the arterial waveform, baroreflex, and δ changes of variables among others and their interactions with each other generating a total of 2.6 million features that are analyzed to predict hypotension. The complexity of the model required to predict hypotension can explain why it performs better than any single variable in predicting impending hypotension.

Given that relatively short durations of hypotension may cause kidney and myocardial injury,[4,15] Futier et al[16] investigated the effects of avoiding hypotension in a protocolized manner keeping subjects' systolic blood pressure within 10% of individual baseline using a noradrenaline infusion after subjects had had their SV optimized using a goal-directed fluid therapy protocol. Maintaining a normalized systolic blood pressure was associated with reduced postoperative organ dysfunction. However, 95% of patients ended up receiving a vasoactive infusion, and the question arises as to how many patients were started on a vasopressor infusion when not hypotensive or likely to be so. Initiating vasoactive treatment in the majority of a surgical population in an aim to avoid hypotension when the event may not occur or when the use of vasoactive medication may not be the appropriate treatment is controversial.

Predictive analytics such as the Hypotension Prediction Index algorithm allow proactive treatment of hypotension (occurring with a high certainty had proactive treatment not been delivered). Whether preemptive treatment and thus avoidance of hypotension will reduce the incidence of postoperative complications is as yet unknown as is the correct treatment protocol for preventing hypotension.

There are mechanisms that are able to predict hypotension in the perioperative period such as HR variability,[17,18] SVV,[19] arterial stiffness,[20] or pulsatility index[21,22]; however, these are commonly static single measurements which have a low sensitivity or are difficult to perform, while the Hypotension Prediction Index provides continuous real-time prediction of the risk of future hypotension from the arterial waveform. Machine learning techniques have been used to predict postinduction hypotension; however, this is only in the first 10 minutes after induction using perioperative data on comorbidities, medications, and demographics.[23] The performance of the model was dependent on the methods used; however, the best performing model had an area under the curve of 0.74 with a positive predictive value of 96% and a negative predictive value of 19%, which was lower than that seen for the Hypotension Prediction Index.

What remains unknown, however, is whether the Hypotension Prediction Index adds incremental value to the clinical judgment of an experienced clinician in predicting hypotension through their recognition of changes in multiple hemodynamic variables over time, situational awareness, and knowledge of patient comorbidities. While this study cannot answer this question, the high incidence and duration of hypotension seen in this cohort and others[6,14] suggest that clinical judgment alone still results in significant time in hypotension. Whether proactive use of a predictive algorithm such as the Hypotension Prediction Index would reduce the incidence or duration is unknown.

The main strength of this study is that it included exclusively patients who had goal-directed fluid therapy as a standard of care, and we recorded and analyzed a large number of commonly measured variables; however, there are a number of limitations. First, this is a retrospective analysis of data and therefore data were not available on the treatment of hypotensive events, and some clinicians had access to the Hypotension Prediction Index information. It is, therefore, likely that a number of impending hypotensive events were treated before they actually occurred. This would weaken the receiver operating characteristic analysis and therefore the true predictive ability of the Hypotension Prediction Index, and the other hemodynamic variables may be underestimated. We attempted to compensate for this when analyzing the event rates by removing data points when sudden rises in MAP occurred thought to be due to interventions. Hypotensive events due to clinical interventions such as laparoscopic insufflation of the abdomen or vascular clamp removal were also unable to be excluded because this algorithm cannot account for these external sources of hypotension. The ability to exclude these events would increase the positive predictive value; however, the current analysis reflects "real world" use of this technology. Second, it is a mixed population of general, vascular, and off-pump cardiac surgery patients in which the cardiac patients may be more prone to more hypotensive episodes. However, exclusion of the cardiac population did not alter the incidence of hypotension, although its duration was slightly reduced. Third, δ analysis of variables has only been presented for a 3-minute timescale; however, analysis of δ timescale of 1, 2, and 5 minutes yielded similar results, which is in agreement with the data in the algorithm derivation paper.[6]

The Hypotension Prediction Index provides real time and continuous prediction of impending hypotension before its occurrence and has superior predictive ability than the commonly measured perioperative hemodynamic variables. As the Hypotension Prediction Index increases, so does the actual event rate, and the time to hypotension decreases. Future work is necessary to show if avoiding intraoperative hypotension using the Hypotension Prediction Index can reduce postoperative complications and improve patient outcome.

DISCLOSURES

Name: Simon James Davies, MD, PhD.
Contribution: This author helped design the study, recruit the patients, collect the data, draft the manuscript, and review the final manuscript.
Conflicts of Interest: S. J. Davies has received honorarium and research funding from Edwards Lifesciences Ltd.
Name: Simon Tilma Vistisen, PhD.
Contribution: This author helped design the study, collect and analyze the data, and review the final manuscript.
Conflicts of Interest: None.
Name: Zhongping Jian, PhD.
Contribution: This author helped design the study, analyze the data, and review the final manuscript.
Conflicts of Interest: Z. Jian is an employee of Edwards Lifesciences Ltd.
Name: Feras Hatib, PhD.
Contribution: This author helped design the study, analyze the data, and review the final manuscript.
Conflicts of Interest: F. Hatib is an employee of Edwards Lifesciences Ltd.
Name: Thomas W. L. Scheeren, PhD.
Contribution: This author helped design the study, recruit the patients, collect the data, and review the final manuscript.
Conflicts of Interest: T. W. L. Scheeren has received honorarium and research funding from Edwards Lifesciences Ltd. He is an associate editor of *Anesthesia & Analgesia*, but had no role in the handling of this manuscript.
This manuscript was handled by: Tong J. Gan, MD.

REFERENCES

1. Vernooij LM, van Klei WA, Machina M, Pasma W, Beattie WS, Peelen LM. Different methods of modelling intraoperative hypotension and their association with postoperative complications in patients undergoing non-cardiac surgery. *Br J Anaesth*. 2018;120:1080–1089.
2. 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.
3. Südfeld S, Brechnitz S, Wagner JY, et al. Post-induction hypotension and early intraoperative hypotension associated with general anaesthesia. *Br J Anaesth*. 2017;119:57–64.
4. 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.
5. 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.
6. Hatib F, Jian Z, Buddi S, et al. Machine-learning algorithm to predict hypotension based on high-fidelity arterial pressure waveform analysis. *Anesthesiology*. 2018;129:663–674.
7. Simera I, Altman DG, Moher D, Schulz KF, Hoey J. Guidelines for reporting health research: the EQUATOR network's survey of guideline authors. *PLoS Med*. 2008;5:e139.
8. Birkhahn RH, Gaeta TJ, Terry D, Bove JJ, Tloczkowski J. Shock index in diagnosing early acute hypovolemia. *Am J Emerg Med*. 2005;23:323–326.
9. De Hert SG, Robert D, Cromheecke S, Michard F, Nijs J, Rodrigus IE. Evaluation of left ventricular function in anesthetized patients using femoral artery dP/dt(max). *J Cardiothorac Vasc Anesth*. 2006;20:325–330.
10. Morimont P, Lambermont B, Desaive T, Janssen N, Chase G, D'Orio V. Arterial dP/dtmax accurately reflects left ventricular contractility during shock when adequate vascular filling is achieved. *BMC Cardiovasc Disord*. 2012;12:13.
11. Cecconi M, Monge García MI, Gracia Romero M, et al. The use of pulse pressure variation and stroke volume variation in spontaneously breathing patients to assess dynamic arterial elastance and to predict arterial pressure response to fluid administration. *Anesth Analg*. 2015;120:76–84.
12. Pinsky MR. Defining the boundaries of bedside pulse contour analysis: dynamic arterial elastance. *Crit Care*. 2011;15:120.
13. Liu H, Li G, Cumberland WG, Wu T. Testing statistical significance of the area under a receiving operating characteristics curve for repeated measures design with bootstrapping. *Journal of Data Science*. 2005;3:257–278.
14. Maheshwari K, Khanna S, Bajracharya GR, et al. A randomized trial of continuous noninvasive blood pressure monitoring during noncardiac surgery. *Anesth Analg*. 2018;127:424–431.
15. Hallqvist L, Granath F, Huldt E, Bell M. Intraoperative hypotension is associated with acute kidney injury in noncardiac surgery: an observational study. *Eur J Anaesthesiol*. 2018;35:273–279.
16. 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.
17. Hanss R, Bein B, Francksen H, et al. Heart rate variability-guided prophylactic treatment of severe hypotension after subarachnoid block for elective cesarean delivery. *Anesthesiology*. 2006;104:635–643.
18. Hanss R, Bein B, Weseloh H, et al. Heart rate variability predicts severe hypotension after spinal anesthesia. *Anesthesiology*. 2006;104:537–545.
19. Juri T, Suehiro K, Tsujimoto S, et al. Pre-anesthetic stroke volume variation can predict cardiac output decrease and hypotension during induction of general anesthesia. *J Clin Monit Comput*. 2018;32:415–422.
20. Alecu C, Cuignet-Royer E, Mertes PM, et al. Pre-existing arterial stiffness can predict hypotension during induction of anaesthesia in the elderly. *Br J Anaesth*. 2010;105:583–588.
21. Kuwata S, Suehiro K, Juri T, et al. Pleth variability index can predict spinal anaesthesia-induced hypotension in patients undergoing caesarean delivery. *Acta Anaesthesiol Scand*. 2018;62:75–84.
22. Sakata K, Yoshimura N, Tanabe K, Kito K, Nagase K, Iida H. Prediction of hypotension during spinal anesthesia for elective cesarean section by altered heart rate variability induced by postural change. *Int J Obstet Anesth*. 2017;29:34–38.
23. Kendale S, Kulkarni P, Rosenberg AD, Wang J. Supervised machine-learning predictive analytics for prediction of postinduction hypotension. *Anesthesiology*. 2018;129:675–688.