# Predicting hypotension in perioperative and intensive care medicine

Saugel, Bernd; Kouz, Karim; Hoppe, Phillip; Maheshwari, Kamal; Scheeren, Thomas W. L.

*Published in:*
Best practice & research. Clinical anaesthesiology

*DOI:*
10.1016/j.bpa.2019.04.001

Best Practice & Research Clinical Anaesthesiology 33 (2019) 189–197

Contents lists available at ScienceDirect

Best Practice & Research Clinical Anaesthesiology

journal homepage: www.elsevier.com/locate/bean

6

# Predicting hypotension in perioperative and intensive care medicine

Bernd Saugel, Professor, Anesthesiology [a, b, *, 1],
Karim Kouz, Resident, Anesthesiology [a, 1],
Phillip Hoppe, Resident, Anesthesiology [a],
Kamal Maheshwari, Staff Anesthesiologist [c],
Thomas W.L. Scheeren, Professor, Anesthesiology [d]

[a] *Department of Anesthesiology, Center of Anesthesiology and Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246, Hamburg, Germany*
[b] *Outcomes Research Consortium, Cleveland, OH, USA*
[c] *Departments of General Anesthesiology and Outcomes Research, Anesthesiology Institute, Cleveland Clinic, 9500 Euclid Avenue — E31, Cleveland, OH, 44195, USA*
[d] *Department of Anesthesiology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, P.O. Box 33.001, 9700 RB, Groningen, the Netherlands*

*Keywords:*
artificial intelligence
machine learning
blood pressure
cardiovascular dynamics
hemodynamic monitoring
hypotension prediction index

Blood pressure is the main determinant of organ perfusion. Hypotension is common in patients having surgery and in critically ill patients. The severity and duration of hypotension are associated with hypoperfusion and organ dysfunction. Hypotension is mostly treated reactively after low blood pressure values have already occurred. However, prediction of hypotension before it becomes clinically apparent would allow the clinician to treat hypotension pre-emptively, thereby reducing the severity and duration of hypotension. Hypotension can now be predicted minutes before it actually occurs from the blood pressure waveform using machine-learning algorithms that can be trained to detect subtle changes in cardiovascular dynamics preceding clinically apparent hypotension. However, analyzing the complex cardiovascular system is a challenge because cardiovascular physiology is highly interdependent, works within complicated networks, and is influenced by compensatory mechanisms. Improved hemodynamic data collection and

* Corresponding author. Department of Anesthesiology, Center of Anesthesiology and Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246, Hamburg, Germany.

*E-mail addresses:* bernd.saugel@gmx.de, b.saugel@uke.de (B. Saugel), karim.kouz@gmail.com, k.kouz@uke.de (K. Kouz), p.hoppe@uke.de (P. Hoppe), maheshk@ccf.org (K. Maheshwari), t.w.l.scheeren@umcg.nl (T.W.L. Scheeren).

[1] These authors contributed equally to the paper.

https://doi.org/10.1016/j.bpa.2019.04.001
1521-6896/

integration will be a key to improve current models and develop new hypotension prediction models.



## Background

Mean arterial pressure is the inflow pressure in most organ systems and – together with organ-specific outflow pressure – the main determinant of organ perfusion pressure. In healthy individuals, blood pressure shows considerable circadian variation but still is kept constant within certain levels. Profound hypotension is common in patients having surgery [1] and in critically ill patients [2] and can result in tissue hypoperfusion and subsequent organ damage. Blood flow autoregulation provides some protection against hypotension-induced hypoperfusion for the brain, heart, and kidney, but perfusion of other organ systems – especially splanchnic organs with weak blood flow autoregulation such as the stomach, small intestine, colon, liver, and pancreas – almost exclusively depends on blood pressure [3]. Therefore, intermittent or continuous blood pressure monitoring using invasive or non-invasive measurement methods is standard of care in perioperative and intensive care medicine to ensure patient safety and optimize perfusion pressure. However, with the currently used blood pressure monitoring methods, only clinically apparent hypotension is recognized that often appears late in the disease process. There is an increasing notion that impending hypotension should be recognized and treated at the earliest stage to reduce the total amount of profound hypotension. In this review, we describe the concept of predicting hypotension that might enable hypotension to be treated pre-emptively before it even occurs, in contrast to the current reactive management.

## Hypotension: impact on outcome

Hypotension is a sign of cardiocirculatory dysfunction, and – because blood pressure is mathematically and physiologically coupled with cardiac output and systemic vascular resistance – it can be caused by low cardiac preload, low afterload, impaired cardiac contractility, or any combination of these factors.

Low blood pressure during surgery that is usually referred to as intraoperative hypotension has a multifactorial etiology and commonly occurs in patients having surgery under general anesthesia [4]. Although intraoperative hypotension is poorly defined [4], it has been shown to be associated with postoperative mortality [5–7], myocardial injury [8–11], acute kidney injury [9,11–14], and stroke [15] in patients undergoing non-cardiac surgery under general anesthesia.

A randomized controlled trial comparing individualized blood pressure targets (based on a patients' baseline resting systolic blood pressure value) with standard care indicates a partial causal relationship between hypotension and postoperative organ dysfunction [16]. Intraoperative hypotension is not a uniform disease but rather a symptom that occurs during different phases in the perioperative care for patients having surgery [17]. A third of hypotension during surgery occurs after induction of general anesthesia before surgical incision and is thus directly related to the induction and maintenance of general anesthesia [13]. Hypotension is also common, profound, and associated with adverse outcomes in patients treated in surgical wards during the first postoperative days [18].

Hypotension also frequently occurs in critically ill patients treated in the intensive care unit. Episodes of hypotension are associated with higher mortality in patients with distributive shock requiring vasopressor therapy [19] and with acute kidney injury in patients with [20] and without sepsis [21]. In patients with sepsis, an increase in the time-weighted average of a mean arterial pressure below 65 mmHg has been shown to be associated with an increase in the risk of in-hospital mortality, acute kidney injury, and myocardial injury [2]. However, the optimal target blood pressure in patients with sepsis as well as in critically ill patients, in general, remains elusive. Additionally, the combined effects of hypotension and vasopressor load remain controversial [22,23].

## Hypotension: treatment strategies

To date, the management of hypotension mainly consists of reactive treatment with vasopressors and fluids after low blood pressure values already have occurred. Monitoring systems in the operating room or the intensive care unit enable numerical and waveform blood pressure data to be processed and displayed continuously in real time. To avoid profound or sustained hypotension, clinicians react to absolute blood pressure threshold values or short-term blood pressure changes. However, low blood pressure values occur late in the process of hemodynamic instability, i.e., when global cardiovascular dynamics are already markedly altered and compensatory mechanisms are exhausted.

Early identification of hypotension or even prediction before it becomes clinically apparent would allow the clinician to apply pre-emptive treatment strategies and thus reduce the incidence or duration of hypotensive episodes. To date, pre-emptive treatment strategies are not well established because the etiology of hypotension is complex and multifactorial. Specific causative pre-emptive treatment of hypotension would require identifying the underlying pathophysiologic cause of impending hypotension, including decreased cardiac preload, cardiac afterload, or myocardial contractility. Pre-emptive treatment strategies could be applied if hypotension could be predicted from clinical data and hemodynamic patterns using machine learning and artificial intelligence. Recently, such algorithms for the prediction of perioperative hypotension have been proposed.

## Machine learning and artificial intelligence – definition and application in medicine

Machine learning, which is a subset of artificial intelligence, enables systems to automatically learn from data and improve from experience without being explicitly programmed. That means that properties of machine learning include the ability to capture a vast number of different variables, called model features. Machine-learning algorithms are used in several medical fields such as identifying and genotyping copy number variations using single nucleotide polymorphism array data [24], rendering medical diagnoses when applied to medical images [25], or predicting bispectral index values produced by target-controlled infusions of propofol and remifentanil [26]. All these applications have the same fundamental problem – they have to deal with a considerable amount of data. This type of "information asset characterized by its high volume, velocity, and variety to require specific technology and analytical method for its transformation into value" is called big data [27]. Due to the expanding use of machine learning and associated techniques, a set of guidelines has been worked up to enable correct use of machine-learning predictive models within clinical settings and to make sure that the models are correctly applied and reported [28].

## Machine learning for predicting hypotension: basic concepts

Imperceptible changes in different physiological variables usually precede clinical hypotension [29,30]. Thus, predicting hypotension using machine learning is not only an intriguing concept but may fundamentally improve patient care in perioperative and intensive care medicine. Clinicians would be able to intervene even before the blood pressure drops to a critical level, thereby preserving organ perfusion. However, for reliable prediction of hypotension, we need to understand the pathophysiology of hypotension during surgery or critical illness. To analyze the patterns of cardiovascular dynamics typically preceding hypotensive episodes, continuous hemodynamic monitoring and real-time analysis using machine learning are needed. First machine-learning-based algorithms for the prediction of hypotension recently became available.

Machine learning can specifically help analyzing vast hemodynamic monitoring data such as heart rate, blood pressure, stroke volume, and cardiac output and complex relationships between these model features, which are imperceptible to human recognition [31]. However, analyzing physiologic systems with machine learning is complex because biological systems are highly interdependent and have developed complicated networks. Beside an intrinsic and complex regulation, physiologic systems react to events such as trauma and disease (and their medical treatment). Each behavior depends on the initial state of the system and even knowing exactly how the physiologic system works and interacts, one would still be unable to accurately predict the behavior of the system in the future. Already subtle changes in the baseline physiologic state can result in considerable variations [29]. This dilemma has been termed the *butterfly effect*, a term from chaos theory [32]. It underlines the problem of physicians to predict patient outcomes despite ingenious monitoring systems and knowledge of physiology and pathophysiology. As most of the observations on our planet, hemodynamic processes also follow nonlinear systems meaning that – in contrast to linear systems – it is impossible to accurately predict their behavior. A central feature of these complex system interactions is the ability of the systems to self-organize spontaneously and by that being robust and resilient [29].

Whenever a hemodynamic variable in the human body changes its value (which is adjusted by specific but not static set points), compensatory mechanisms turn on. Most of the times, these mechanisms, such as baroreflex [33,34] or renin-angiotension-aldosterone-system activation, cause subtle hemodynamic changes resulting in unique dynamic patterns in arterial blood pressure waveforms. An example of this complex interplay of physiologic feedback loops is heart rate variability, which has been shown to decrease before a hypotensive event occurs [35]. Analogically, a broad number of clinical variables and waveforms exist that underlie natural variability caused by various compensatory mechanisms that try to maintain hemodynamics stable (e.g., heart rate and arterial blood pressure) [36,37]. Analyzing these subtle changes in cardiovascular dynamics is complex and challenging. First, most of these changes are hard to recognize at the bedside because of their complexity and subtlety. Second, most of these changes develop and progress slowly and therefore can only be seen by analyzing them over a longer period of time [30]. Third, a lot of the compensatory mechanisms create complex physiological associations and dynamic links between different hemodynamic variables and waveforms, which are even more difficult to identify by routine bedside monitoring.

Artificial intelligence, in terms of machine learning and complex extraction techniques, now gives us the opportunity for early detection of subtle hemodynamic information preceding hemodynamic instability [29,30,38,39]. Machine-learning methods are powerful tools that can be used to identify early stages of instability even before a hypotensive event clinically occurs [40,41].

## Machine learning for predicting hypotension: recent advances and future directions

Hatib et al. [42] recently developed an algorithm for real-time prediction of hypotension, called "hypotension prediction index" (HPI). It uses machine-learning models based on the continuous analysis of a large number of hemodynamic features extracted from the arterial blood pressure waveform. The hypotension prediction index is a unit less number that ranges from 0 to 100. The higher the number, the higher is the probability that hypotension will occur in the near future and the shorter is the time for its occurrence. For the development of the algorithm (model training and cross-validation to adjust the model), waveforms obtained in a cohort of 1334 patients treated in the operating room and the ICU were used. The external validation cohort consisted of 204 patients of the University of California at Irvine Medical Center whose arterial blood pressure waveforms were recorded in the operating room. For each data set, periods of hypotension (mean arterial pressure <65 mmHg for at least 1 min) and nonhypotension (mean arterial pressure >75 mmHg) were annotated to serve as the training data set. The waveforms were then analyzed to extract waveform features by dividing the arterial blood pressure waveform into unique beats and separated each beat into five phases (systolic phase, diastolic phase, systolic rise phase, systolic decay phase, and overall decay phase). For each phase, several features were analyzed and calculated: arterial blood pressure waveform time, amplitude, area, and slope features; FloTrac algorithm features (FloTrac; Edwards Lifesciences, Irvine, CA); CO-Trek features obtained from the ClearSight system (Edwards Lifesciences); complexity features; baroreflex features; variability features; spectral features; "delta change" features; and combinatorial features. In this way, 3022 individual features were obtained. Performing receiver operating characteristic (ROC) analysis for each of the features, 51 individual features – so-called base features – were extracted. Creating combinatorial features finally ended up to 2,606,147 combinatorial waveform features in total. Statistically assessing the collected features or a combination of these using machine-learning techniques resulted in a prediction model for hypotension, which was validated on the waveforms of the second patient cohort. After validating the algorithm, the model was able to predict arterial hypotension with a sensitivity of 88% and a specificity of 87% 15 min before a hypotensive event.

This landmark study shows the potential of the use of artificial intelligence for analyzing and predicting cardiovascular dynamics. However, the study has several limitations. First, hypotensive events caused by clinical interventions (e.g., laparoscopic insufflation, liver manipulation, or vascular clamping or unclamping) were not included in the study, and thus, the model might not be able to predict hypotensive events due to such interventions. Second, the question of whether the algorithm can predict hypotension during induction of anesthesia remains unanswered, as it was not formally tested in this study. Next, the algorithm has been trained and developed based on records of operating room and intensive care unit patients, while it has been validated in surgical patients. Furthermore, data streams were not analyzed in real time to predict hypotension, and a "gray zone" for mean arterial pressure (ranging from 65 to 75 mmHg) was applied during the development of the algorithm to increase precision by using a binary model.

Recently, the algorithm developed by Hatib et al. [42] became commercially available as a feature of the EV1000 and Hemosphere clinical monitoring platforms (Edwards Lifesciences). The HPI value, ranging from 0 to 100, is calculated every 20 s and displayed on the monitor. It represents the probability that a patient will develop a hypotensive event, defined as a mean arterial pressure of less than 65 mmHg for at least 1 min. Once HPI exceeds the value of 85, an audible alarm sounds. When HPI exceeds the upper limit for two consecutive calculations, a pop-up window appears automatically, prompting the clinician to use a secondary screen, which displays more hemodynamic information of the patient (hemodynamic variables reflecting preload, afterload, and contractility), to help the clinician get insight into probable causes and causative treatment options for the hypotensive event. Refinements of the algorithm will probably increase the predictive capabilities of the HPI in the future. This may include enhancing the predictive capabilities in the blood pressure gray zone and the prediction of hypotension due to anesthesia induction or other clinical interventions. Another innovation expected in the near future probably is the use of the HPI on noninvasively assessed arterial blood pressure waveforms. Even if this new technique seems to be a promising tool, the clinical use of the HPI needs to be meticulously validated, and outcome studies are needed.

Ranucci et al. [43] tested the discrimination and calibration properties of the HPI in a retrospective study with hemodynamic data of 23 patients undergoing cardiac and major vascular surgeries. They treated their patients in the intraoperative phase based on routine hemodynamic variables (heart rate, mean arterial pressure, cardiac index, central venous pressure, systemic vascular resistance, and stroke volume variation) and echocardiographic data when available. After analyzing the collected data, they investigated the predictive capabilities of the HPI observed 5 and 7 min ($HPI_{5\text{-}7}$) before the hypotensive event, defined as mean arterial pressure <65 mmHg lasting for at least 1 min, using an ROC analysis. They identified the best cut-off value at an $HPI_{5\text{-}7}$ of 56 (sensitivity 79%, specificity 63%), with a low positive predictive value of 9.8% for hypotensive events. At an HPI value of 85, the negative predictive value was 97.6%. The positive predictive value was too low (12.6%) to trigger hemodynamic interventions by the clinician but is useful as an early warning signal. For HPI values >98, the probability of an upcoming hypotensive event after 5–7 min was 64%, which may generally be high enough to trigger adequate interventions potentially preventing the event. One major limitation in this study might be that the knowledge of the study goal might have influenced the care by the attending anesthesiologist; anesthesiologists might probably have prevented or corrected altered hemodynamic patterns before a hypotensive event occurred. Furthermore, they might even have "treated" expected hypotensive events that probably would not have occurred, resulting in overtreatment. Next, the time window of this study (5–7 min) differs from the window (15–20 min) suggested when the HPI algorithm was designed. Therefore, clinical studies investigating time windows larger than 5–7 min are needed. Additionally, it would be interesting to know how differences in the experience of the attending anesthesiologist influence the pre-emptive treatment of hypotensive events in patients with and without HPI monitoring.

Davies et al. [44] carried out an HPI validation study to investigate the diagnostic ability of the HPI algorithm to predict intraoperative hypotension in comparison to other routinely collected hemodynamic variables during the perioperative period. In a retrospective study, they analyzed 292,025 perioperative data points collected with the EV1000 monitoring system containing the HPI software

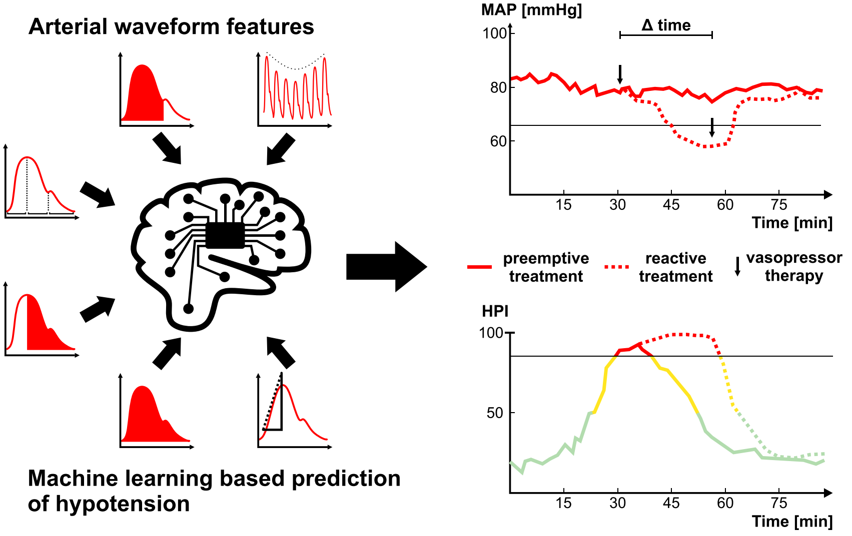


**Fig. 1.** Pre-emptive treatment of upcoming hypotensive events based on the hypotension prediction index (HPI) vs. reactive treatment of hypotension that already became clinically apparent. The HPI is based on a machine learning algorithm analyzing features of the arterial blood pressure waveform. In this example, pre-emptive treatment triggered by an HPI of 85 helps to avoid hypotension.

in 255 patients having major surgery (major abdominal, vascular, or off-pump coronary artery bypass surgery). These data were downloaded from the monitor as follows: HPI, cardiac output, mean arterial pressure, stroke volume, stroke volume variation, heart rate, pulse pressure, pulse pressure variation, systemic vascular resistance, and arterial blood pressure waveforms. From the latter, shock index, modified shock index, contractility, and dynamic arterial elastance were computed. To evaluate the performance of HPI in predicting hypotension, an ROC analysis was performed (again based on the definition of a hypotensive event as a mean arterial pressure <65 mmHg for at least 1 min). This analysis was used to evaluate the performance of the change in mean arterial pressure to predict hypotension, as well as absolute values of mean arterial pressure, cardiac output, stroke volume, pulse pressure, heart rate, stroke volume variation, pulse pressure variation, and systemic vascular resistance. The HPI algorithm reliably predicted a hypotensive event up to 15 min before its occurrence, and the predictive capabilities of the HPI were superior (AUC 0.879, 95% confidence interval 0.879 to 0.880; sensitivity 81%; specificity 81%) to all other static hemodynamic variables or their dynamic changes. However, some limitations of the study have to be mentioned. First, the data have been analyzed retrospectively, and therefore, data on HPI-guided treatment of (upcoming) hypotensive events were not available. Next, some clinicians might have had access to the HPI information, which would weaken the ROC analysis in case of anticipatory action. Further, hypotensive events due to clinical interventions (i.e., laparoscopic insufflation) were not excluded. Future studies should evaluate the HPI algorithm in real time at the bedside.

Kendale et al. performed a study on the prediction of postinduction hypotension, i.e., low blood pressures after induction of general anesthesia [45]. For this purpose, they developed a machine-learning model for the prediction of postinduction hypotension, i.e., a mean arterial pressure <55 mmHg on any noninvasive or invasive blood pressure measurement within 10 min after the time of induction of general anesthesia. The prediction algorithm was based on demographic, biometric, and clinical factors potentially contributing to the development of postinduction hypotension. In a single large academic institution, these factors were extracted from the electronic health record of 13,323 patients having general anesthesia (training set: 9326 cases, test set 3997 cases); the factors were age, sex, body mass index, preoperative medical comorbidities (coronary artery disease, hypertension, congestive heart failure, atrial fibrillation, chronic kidney disease, asthma, chronic obstructive pulmonary disease, gastroesophageal reflux disease, obstructive sleep apnea, diabetes mellitus, and aortic stenosis), preoperative medications (grouped into subclasses), time of surgery, American Society of Anesthesiologists physical status score, intraoperative medications, and intraoperative vital signs and ventilator data. The authors did not use waveform data from the monitor for their prediction model. The final model used a gradient boosting machine that demonstrated strong discrimination in the training (ROC 0.76, 95% confidence interval 0.75 to 0.77) and testing (ROC 0.74, 95% confidence interval 0.72 to 0.77) sets. To further improve the algorithm, it might be useful to incorporate more data in the machine-learning model such as vital signs or preoperative lab values.

## Conclusions

Blood pressure is the main determinant of organ perfusion. Profound hypotension is common in patients having surgery and who are critically ill, and is associated with hypoperfusion and organ failure. To date, hypotension is treated reactively after low blood pressure values have already occurred. Early identification of impending hypotension or even prediction before it becomes clinically apparent would allow the clinician to treat hypotension pre-emptively and thus reduce the incidence or duration of hypotensive episodes (Fig. 1). Algorithms developed using machine learning have recently been proposed for the prediction of hypotension. Machine learning, a subset of artificial intelligence, enables subtle changes in cardiovascular dynamics – that precede clinically apparent hypotension – to be recognized and analyzed and hypotension to be predicted minutes before it actually occurs. However, analyzing the cardiovascular system using artificial intelligence is complex because cardiovascular physiology is highly interdependent, works within complicated networks, and is influenced by multiple compensatory mechanisms. Recently, an algorithm for real-time prediction of hypotension using machine-learning models based on the continuous analysis of features of the arterial blood pressure waveform has been proposed. The algorithm has been shown to be able to predict hypotension reliably several minutes before a hypotensive event becomes clinically apparent in validation studies in patients having surgery [42–44].

## Declaration of interest

BS collaborates with Pulsion Medical Systems SE (Feldkirchen, Germany) as a member of the medical advisory board and has received institutional restricted research grants, honoraria for giving lectures, and refunds of travel expenses from Pulsion Medical Systems SE. BS has received research support and honoraria for giving lectures from Edwards Lifesciences (Irvine, CA, USA). BS has received institutional restricted research grants, honoraria for giving lectures, and refunds of travel expenses from CNSystems Medizintechnik GmbH (Graz, Austria). BS has received institutional restricted research grants, honoraria for consulting, and refunds of travel expenses from Tensys Medical Inc. (San Diego, CA, USA). BS has received institutional restricted research grants from Retia Medical LLC. (Valhalla, NY, USA). BS has received honoraria for giving lectures from Philips Medizin Systeme Böblingen GmbH (Böblingen, Germany).

KK has no conflicts of interest to disclose.

PH has no conflicts of interest to disclose.

KM received research grants and honoraria for consulting from Edwards Lifesciences.

TS received research grants and honoraria from Edwards Lifesciences and Masimo Inc. (Irvine, CA, USA) for consulting and for giving lectures. TS received honoraria from Pulsion Medical Systems SE for giving lectures.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Practice points**

- Perioperative hypotension and hypotensive events in critically ill patients are common and associated with hypoperfusion and organ failure.
- Low blood pressure values occur late in the development of hemodynamic instability, i.e., when global cardiovascular dynamics are already markedly altered and compensatory mechanisms are exhausted.
- The use of artificial intelligence (machine learning) gives us the opportunity to predict hypotensive events and might enable pre-emptive rather than reactive treatment strategies to be used.

**Research agenda**

- Refinements and further developments of existing algorithms for the prediction of hypotensive events will probably increase the predictive capabilities of machine-learning models in the future.
- The prediction of hypotensive events based on noninvasively assessed arterial blood pressure waveforms will become possible but needs to be meticulously validated.
- Studies investigating whether prediction of hypotension can actually improve the quality of care or patient-centered outcomes are needed.

## Acknowledgments

None.

## References

*[1] Wesselink EM, Kappen TH, Torn HM, et al. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. Br J Anaesth 2018;121:706–21.
*[2] Maheshwari K, Nathanson BH, Munson SH, et al. The relationship between ICU hypotension and in-hospital mortality and morbidity in septic patients. Intensive Care Med 2018;44:857–67.
[3] Meng L, Wang Y, Zhang L, et al. Heterogeneity and variability in pressure autoregulation of organ blood flow: lessons learned over 100+ years. Crit Care Med 2019;47:436–48.
[4] Bijker JB, van Klei WA, Kappen TH, et al. Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. Anesthesiology 2007;107:213–20.
[5] Monk TG, Saini V, Weldon BC, et al. Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg 2005;100:4–10.
[6] Mascha EJ, Yang D, Weiss S, et al. Intraoperative mean arterial pressure variability and 30-day mortality in patients having noncardiac surgery. Anesthesiology 2015;123:79–91.
[7] Bijker JB, van Klei WA, Vergouwe Y, et al. Intraoperative hypotension and 1-year mortality after noncardiac surgery. Anesthesiology 2009;111:1217–26.
[8] Sessler DI, Khanna AK. Perioperative myocardial injury and the contribution of hypotension. Intensive Care Med 2018;44:811–22.
[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] van Waes JA, van Klei WA, Wijeysundera DN, et al. Association between intraoperative hypotension and myocardial injury after vascular surgery. Anesthesiology 2016;124:35–44.
*[11] 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;119:507–15.
[12] Sun LY, Wijeysundera DN, Tait GA, et al. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. Anesthesiology 2015;123:515–23.
[13] Maheshwari K, Turan A, Mao G, et al. The association of hypotension during non-cardiac surgery, before and after skin incision, with postoperative acute kidney injury: a retrospective cohort analysis. Anaesthesia 2018;73:1223–8.

[14] Mizota T, Hamada M, Matsukawa S, et al. Relationship between intraoperative hypotension and acute kidney injury after living donor liver transplantation: a retrospective analysis. J Cardiothorac Vasc Anesth 2017;31:582–9.
[15] Bijker JB, Persoon S, Peelen LM, et al. Intraoperative hypotension and perioperative ischemic stroke after general surgery: a nested case-control study. Anesthesiology 2012;116:658–64.
*[16] Futier E, Lefrant JY, Guinot PG, et al. 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;318:1346–57.
*[17] Sudfeld 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.
[18] Sessler DI, Meyhoff CS, Zimmerman NM, et al. Period-dependent associations between hypotension during and for four days after noncardiac surgery and a composite of myocardial infarction and death: a substudy of the POISE-2 trial. Anesthesiology 2018;128:317–27.
[19] Vincent JL, Nielsen ND, Shapiro NI, et al. Mean arterial pressure and mortality in patients with distributive shock: a retrospective analysis of the MIMIC-III database. Ann Intensive Care 2018;8:107.
[20] Poukkanen M, Wilkman E, Vaara ST, et al. Hemodynamic variables and progression of acute kidney injury in critically ill patients with severe sepsis: data from the prospective observational FINNAKI study. Crit Care 2013;17:R295.
[21] Izawa J, Kitamura T, Iwami T, et al. Early-phase cumulative hypotension duration and severe-stage progression in oliguric acute kidney injury with and without sepsis: an observational study. Crit Care 2016;20:405.
[22] Leone M, Asfar P, Radermacher P, et al. Optimizing mean arterial pressure in septic shock: a critical reappraisal of the literature. Crit Care 2015;19:101.
[23] Lamontagne F, Day AG, Meade MO, et al. Pooled analysis of higher versus lower blood pressure targets for vasopressor therapy septic and vasodilatory shock. Intensive Care Med 2018;44:12–21.
[24] Zhang Z, Cheng H, Hong X, et al. EnsembleCNV: an ensemble machine learning algorithm to identify and genotype copy number variation using SNP array data. Nucleic Acids Res 2019;(47):e39.
[25] Erickson BJ, Korfiatis P, Akkus Z, et al. Machine learning for medical imaging. Radiographics 2017;37:505–15.
[26] Lee HC, Ryu HG, Chung EJ, et al. Prediction of bispectral index during target-controlled infusion of propofol and remifentanil: a deep learning approach. Anesthesiology 2018;128:492–501.
[27] De Mauro A, Greco M, Grimaldi M. A formal definition of Big Data based on its essential features. Libr Rev 2016;65:122–35.
[28] Luo W, Phung D, Tran T, et al. Guidelines for developing and reporting machine learning predictive models in biomedical research: a multidisciplinary view. J Med Internet Res 2016;18:e323.
*[29] Pinsky MR. Complexity modeling: identify instability early. Crit Care Med 2010;38:S649–55.
[30] Pinsky MR, Dubrawski A. Gleaning knowledge from data in the intensive care unit. Am J Respir Crit Care Med 2014;190:606–10.
[31] Mathis MR, Kheterpal S, Najarian K. Artificial intelligence for anesthesia: what the practicing clinician needs to know: more than black magic for the art of the dark. Anesthesiology 2018;129:619–22.
[32] Dooley K. The butterfly effect of the “butterfly effect”. Nonlinear Dyn Psychol Life Sci 2009;13:297–388.
[33] Westerhof BE, Gisolf J, Stok WJ, et al. Time-domain cross-correlation baroreflex sensitivity: performance on the EUROBAVAR data set. J Hypertens 2004;22:1371–80.
[34] Zavodna E, Honzikova N, Hrstkova H, et al. Can we detect the development of baroreflex sensitivity in humans between 11 and 20 years of age? Can J Physiol Pharmacol 2006;84:1275–83.
[35] Padley JR, Ben-Menachem E. Low pre-operative heart rate variability and complexity are associated with hypotension after anesthesia induction in major abdominal surgery. J Clin Monit Comput 2018;32:245–52.
[36] Pagani M, Somers V, Furlan R, et al. Changes in autonomic regulation induced by physical training in mild hypertension. Hypertension 1988;12:600–10.
[37] de Boer RW, Karemaker JM, Strackee J. On the spectral analysis of blood pressure variability. Am J Physiol 1986;251:H685–7.
[38] Guillame-Bert M, Dubrawski A, Wang D, et al. Learning temporal rules to forecast instability in continuously monitored patients. J Am Med Inform Assoc 2017;24:47–53.
[39] Hravnak M, Chen L, Bose E, et al. Artifact patterns in continuous noninvasive monitoring of patients. Intensive Care Med 2013;39:S405.
[40] Convertino VA, Grudic G, Mulligan J, et al. Estimation of individual-specific progression to impending cardiovascular instability using arterial waveforms. J Appl Physiol (1985) 2013;115:1196–202.
[41] Convertino VA, Moulton SL, Grudic GZ, et al. Use of advanced machine-learning techniques for noninvasive monitoring of hemorrhage. J Trauma 2011;71:S25–32.
*[42] Hatib F, Jian Z, Buddi S, et al. Machine-learning algorithm to predict hypotension based on high-fidelity arterial pressure waveform analysis. Anesthesiology 2018;129:663–74.
*[43] Ranucci M, Barile L, Ambrogi F, et al. Discrimination and calibration properties of the hypotension probability indicator during cardiac and vascular surgery. Minerva Anestesiol 2018 [epub ahead of print].
*[44] Davies SJ, Vistisen ST, Jian Z, et al. Ability of an arterial waveform analysis-derived hypotension prediction index to predict future hypotensive events in surgical patients. Anesth Analg 2019 [epub ahead of print].
*[45] Kendale S, Kulkarni P, Rosenberg AD, et al. Supervised machine-learning predictive analytics for prediction of post-induction hypotension. Anesthesiology 2018;129:675–88.